Infectious Diseases in the Intensive Care Unit

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Puneet Khanna
Editors

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FOREWORD

Infection is a dreaded word in the intensive care unit. Although many patients are admitted to the ICU with infections such as pneumonia, meningitis, or sepsis; a substantial number of patients with non-infectious disorders develop life-threatening infections during their stay in the ICU. Thus, effective management of infections is pivotal for successful outcomes. Intensivists need expertise in the diagnosis, treatment, and prevention of variety of infectious diseases.

The infectious diseases encountered in the critical care setting are some of the most severe and often difficult to diagnose and treat. Critical decisions need to be made within a short span of time. The intensivist's task is also becoming increasingly complicated given the alarming milieu of "bad bugs, no drugs", an aging and more immunocompromised patient population, and a wide array of sophisticated but complex diagnostic modalities. Sharp clinical acumen and awareness of availability and optimal use of the latest technology is essential. This book is targeted for critical care practitioners, the majority of whom are not trained in infectious diseases. It is written by clinicians with a vast experience in infectious diseases in critical care and will provide valuable information required in day-to-day practice.

This text is unique in its structure and organization. Comprehensive yet succinct, it discusses all clinical infectious diseases from pneumonia and empyema to central nervous system and antibiotic-related infections. Specific chapters focus on special ICU problems, such as central venous catheter infections, nosocomial pneumonias, endocarditis, C. difficile infection, etc. The book covers special situations in the ICU like tropical diseases, cirrhosis, burns, transplants, tuberculosis etc.

Critical care medicine is becoming more and more technology based; however, the clinical judgement and the knowledge when to order and how to interpret a test is quintessential in the ICU. Formal training of the intensivist in ID has strong potential for synergy in patient care, clinical and epidemiologic research, and the design and execution of control strategies for epidemics/ pandemics.

I congratulate Dr Manish Soneja and Dr Puneet Khanna and their coauthors on the production of this excellent text. It will help guide critical care physicians, ID professionals and their trainees in day to day management and seeing the incredible utility of this book in critical care practice.

14/7/2020

(Prof. Randeep Guleria)

Contents

About the Editors

Manish Soneja graduated from Calcutta Medical College and received his MD in Medicine from AIIMS, New Delhi. Presently, he is an Additional Professor at the Department of Medicine, AIIMS, New Delhi and has a keen interest in infectious diseases and critical care. He played a key role in launching the DM Infectious Diseases program at AIIMS, the first of its kind in India. He has authored several peer-reviewed publications and has delivered numerous conference presentations on topics in infectious disease and critical care.

Puneet Khanna received his MBBS from Kasturba Medical College, Mangalore and completed his MD in Anaesthesiology at AIIMS, New Delhi. He is working as an Associate Professor at the Department of Anaesthesiology, Pain Medicine and Critical care at AIIMS, New Delhi. He was previously an Assistant Professor at the Department of Anaesthesia, PGIMER, Chandigarh. He has published in several prominent national and international journals and has contributed chapters to Indian and international textbooks. Most recently, he published a book on Critical Care Sonography. His research interests include obstetric anaesthesia, translational research, critical care, paediatric anaesthesia, and post-op cognition.

Fever in Intensive Care Unit

1

Ghan Shyam Pangtey and Rajnikant Prasad

1.1 Introduction

The development of fever in a critically ill patient in ICU should not trigger panic, but it should be considered as a sign, which requires appropriate attention and management. Fever is commonly a physiological expression of host response to infectious or non-infectious agents. Fever is also considered to be host defense against external exposure and the raised body temperature helps in better immune response by promoting synthesis of antibodies, cytokines, activated T cells, polymorphs, and macrophages. There is some medical evidence to suggest, raised body temperature may be harmful in patients with acute brain injury and in patients with compromised cardio-respiratory reserve (e.g., cardiac arrest) and pharmacological treatment in these critically ill patient is beneficial. Fever should also be treated in patient who complains of discomfort due to high body temperature.

For an intensivist, fever is most often the starting point for detailed clinical evaluation and prompts him to initiate important diagnostic and treatment decisions. As our knowledge of pathogenesis of fever is expanding along with availability of better diagnostic tools, the perimeter of fever is expanding well beyond bacterial infections. Fungal, viral, and immunological etiologies of fever are now well known and not uncommon. Sometimes a simple drug fever may perplex an intensivist, leading to extensive unfruitful investigations. We will discuss about various infectious and non-infectious causes of fever and briefly discuss the approach to fever management in ICU care.

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1.2 Definition of Fever

The normal body temperature varies with the time of measurement as well as by the method of measurement, the body temperature of approximately 37 °C (98.6 °F) is considered to be normal. The definition of fever is also arbitrary considering the time of day and method of measurement. The most accepted definition of fever in ICU by 2008 Infectious Disease Society of America (IDSA) and American College of Critical Care Medicine (ACCM) is temperature of >38.3 °C (101 °F). This definition has several caveats as it may not be true for the immunocompromised patients, in elderly, patients on immunosuppressant therapy (e.g., corticosteroids), pediatric population, and severe form of sepsis where hypothermia may be the presenting sign instead of fever.

1.3 Measurement of Fever

The fever can be measured by central and peripheral thermometers. Their indications, advantages, disadvantages, and accuracy are given in the Table 1.1. The pulmonary artery catheter based core body temperature measurement is the gold standard and most accurate method, but it is not a feasible method in ICU. The reason includes non-availability of resources, requirement of technical competence, trained and experienced manpower and of course high cost. The peripheral thermometry is still extensively utilized in most of the ICU, although it is less reliable, with average sensitivity and specificity being 64% and 96%, respectively, as compared to central thermometry.

As an intensivist, the dilemma of relying upon central verses peripheral thermometry do exist, especially in resource poor countries. One may prefer central thermometry if accurate measurement is necessary (hypothermia, neutropenic sepsis) or if the temperature is not fitting well with clinical condition. In rest of situation the peripheral thermometry is appropriate.

1.4 Etiopathogenesis of Fever

Fever or pyrexia in human being is thought to be a protective adaptive response secondary to release of cytokines in the circulation. Although the exact mechanism of cytokine release is not understood but it is thought to be related to endocrine and immune mediated. Heat is generated by chemical reactions during catabolism of

Table 1.1 Methods of temperature measurements in intensive care unit

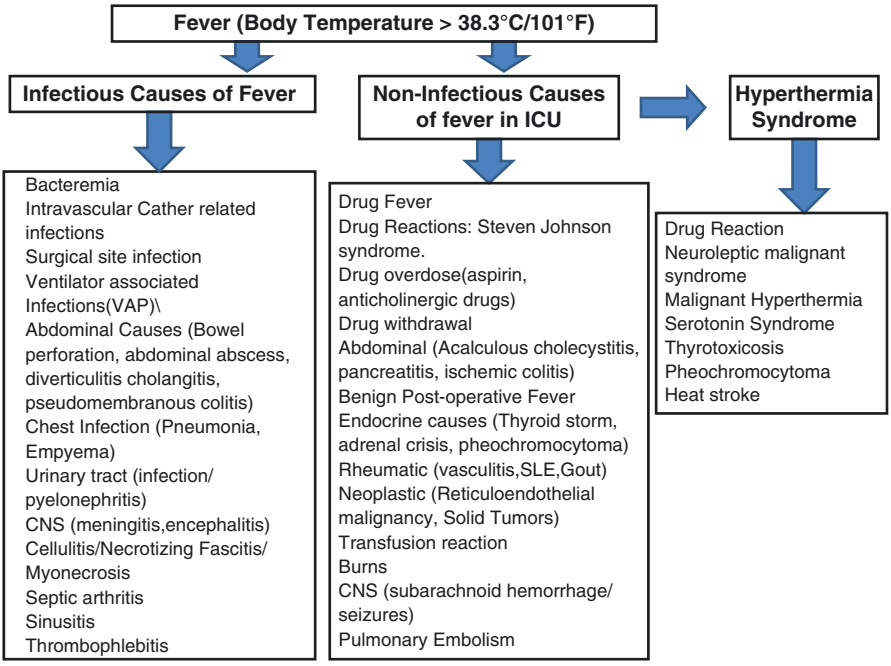
Accuracy	Method of temperature measurement
Most accurate	Pulmonary artery catheter, esophageal probe, bladder probe, rectal probe
Less accurate	Oral, temporal artery probe
Least accurate	Axiliary, tympanic membrane, chemical dot

nutrient inside the cells. Human body generates a basal metabolic rate as well as basal heat production to maintain optimum cell function, and this generated heat is distributed to the whole body by circulatory system. The thermoregulation and control of body temperature is done meticulously by preoptic region of nervous system (hypothalamus, limbic system, lower brainstem, reticular formation, spinal cord, and sympathetic ganglia). The temperature sensitive area in this preoptic region regulates body temperature according to feedback signals as received from the peripheral sensors (skin) and core sensors of body. There are cold and warm sensing neurons in this region, which respond in a way to keep the body temperature in balance and at a set temperature.

Fever has been documented in up to 2/3rd of intensive care unit admissions and is commonly due to infections. Studies have shown that patient with fever in ICU setting is associated with higher mortality, increased length of stay, increased cost of therapy, and poorer outcome, especially in patients with head injury, subarachnoid hemorrhage (SAH), and pancreatitis. However, in few studies, fever in infectious diseases has been associated with less hospital mortality, and considered to be adaptive response to infection. Therefore, the pathophysiologic importance of process of fever is still incompletely understood and controversial.

The etiology of fever in ICU can be divided into infectious or non-infectious in origin (Table 1.2). The proportion of infectious versus non-infectious cause

Table 1.2 Infectious and non-infectious causes of fever



of fever in ICU is highly variable depending on population being studied, type of ICU, and definition of fever being used. The various studies on ICU infections suggest the relative frequency of infectious fever between 50 and 60%. The distinction between infectious and non-infectious fever is challenging for every intensivist. Few studies suggest the magnitude of fever or absolute body temperature may help in differentiation in few situations, in contrary to it others scientists are not fully convinced with importance of absolute temperature. Many experts believe, fever with temperatures between 38.3 °C (101 °F) and 38.8 °C (101.8 °F) can be due to infectious/non-infectious source, therefore not useful in differentiation; while patients with fever between 38.9 °C (102 °F) and 41 °C (105.8 °F) can be assumed to be infectious; patients with very high fever ≥41.1 °C (106 °F) are commonly non-infectious in origin (drug fever, hyperthermia, etc.)

1.5 Infectious Causes of Fever

The common infectious causes of fever in ICU includes ventilator associated pneumonia (VAP), central line associated blood stream infection (CLABSI), catheter related UTI, surgical site infections, and sinusitis. The few important infectious causes of fever in ICU will be discussed in next section.

Ventilator Associated Pneumonia (VAP) Pneumonia developing after >48 h of ventilatory care is called VAP. The triad of VAP consists of new or increase in pulmonary infiltrates on chest radiograph, increase or purulence of tracheobronchial secretions, and leukocytosis.

Central Line Associated Blood Stream Infection (CLABSI) Long term intravascular catheters are commonly associated with fever in ICU patients, who need central line for nutrition, fluid, chemotherapy, or antibiotics. They frequently present as uncomplicated fever without any localizing signs, but alternatively they may present with local abscess or visible purulent secretions from the catheter insertion site. Other manifestations include septicemia with or without multi organ failure or suppurative thrombophlebitis, endocarditis, or septic abscesses. The following points regarding indwelling catheter should be remembered:

1. There is increased use of iv devices (central and peripheral) for short/long term therapeutic goals.
2. Look daily at insertion site for local and possible systemic infection.
3. Culture of pus/discharge at insertion site is not routinely recommended; however, if done, it has got negative predictive value.
4. Please remember to remove iv catheter as soon it is not needed.

Viral Infections Epidemiological studies show that the prevalence of viral respiratory tract infections can be as high as 41% in critically ill patients admitted to the ICU with a suspected CAP, and up to 34% in HAP. It is unclear if all patients admitted to the ICU with a suspected CAP should be tested for respiratory viruses. There are no recommendations for virus testing in patients admitted to the ICU due to HAP. The difficulty is that clinical signs and symptoms are rarely sufficient to make a specific diagnosis of a viral infection.

It is therefore a combination of clinical syndrome together with epidemiologic clues and specific laboratory tests which helps in arriving a diagnosis. Documented viral infections occur in up to 45% of episodes of exacerbation of COPD. Frequently identified viruses in acutely ill COPD patients are rhinoviruses, parainfluenza viruses, coronaviruses, and influenza viruses type A and B. In severely ill adult patients requiring hospitalization and mechanical ventilation, influenza viruses and coronaviruses are most common pathogens.

Fungal Infections Contrary to popular believes that fungal infections occur in immunocompromised patients, there is growing body of evidence that suggest intensive care per se predisposes to fungal infections. The important factors for micro invasion are: prolonged ICU stay (>7 days), parenteral antibiotics use, total parenteral nutrition, major abdominal surgery, vascular access, patients with acute kidney injury. The preexisting conditions like diabetes, burns, prematurity, and neutropenia make fungal infections more likely.

Sinusitis The common cause of sinusitis is anatomic obstruction of ostia draining from sinuses. Persons with deviated nasal septum (DNS) are more prone to some degree of chronic sinusitis. The clinical diagnosis of sinusitis suspected by purulent nasal discharge, fever, and malodourous breath. The ICU patients pose a different problem as many of them are intubated and therefore cannot be assessed routinely for headache, pain, or purulent discharge. In addition, a nasal intubation, orofacial trauma, fracture base of skull, and nasopharyngeal hematomas all contribute to sinusitis. A combination of CT scan along with nasal endoscopy increases diagnostic accuracy as the latter one helps getting the sinus fluid for examination. Regarding pathogens, pseudomonas accounts for 60% infections, *S. aureus* and streptococcus are implicated in 33% cases.

1.6 Non-infectious Causes of Fever

There are several non-infectious causes of fever in ICU. It is good practice to separate the hyperthermia syndrome from other non-infectious cause of fever as they usually present with very high absolute temperature and do not respond to antipyretics therapy, and instead need physical therapy for management. In next section, we

will discuss common causes of hyperthermia and few important causes of non-infectious fever in ICU.

1.6.1 Hyperthermia

Distinction between hyperthermia and fever is required for better management. The very high absolute body temperature which exceeds >41.0 °C and has no response with pharmacological treatment distinguishes between hyperthermia syndrome and fever/pyrexia. In hyperthermia syndrome, there is unregulated rise in body temperature associated with failure of thermoregulatory homeostasis. In routine fever, the adaptive mechanism resets the thermostat, leading to normalization of temperature after sometime. Malignant hyperthermia, neuroleptic malignant syndrome (NMS), serotonin syndrome secondary to antipsychotic drugs, heat stroke, and endocrine cause (thyrotoxicosis, pheochromocytoma, adrenal crisis, etc.) are common causes of hyperthermia (Table 1.2). Malignant hyperthermia occurs in genetically susceptible individuals and associated with use of anesthetic agents (e.g., halothane, succinylcholine, etc.) where dysregulation of intracellular calcium metabolism leads to increased skeletal muscle activity resulting in muscle rigidity, metabolic acidosis, and hyperthermia. The malignant hyperthermia usually occurs immediately after use of culprit anesthetic agents, but uncommonly it may occur up to 24 h later, especially if steroid has been used preoperatively. Dantrolene sodium inhibits calcium ion release from skeletal muscle by antagonizing ryanodine receptor on sarcoplasmic reticulum. It is the drug of choice for malignant hyperthermia as well as for neuroleptic malignant syndrome (NMS) and can be life-saving in critically ill patients. Neuroleptic malignant syndrome develops commonly in patients on antipsychotic (haloperidol) medicines. It is associated with excessive skeletal muscle activity leading to high fever, muscle rigidity, and raised creatinine phosphokinase enzymes levels. The supportive care to reduce body temperature with cold blankets and ice bath is usually required in critically ill patients of hyperthermia in ICU.

Drug Fever Medicines may precipitate fever owing to their pharmacological properties. They may induce fever by allergic/anaphylactic/hypersensitivity reactions, inducing fever, decreasing heat dissipation or altering thermoregulatory mechanism, and inducing cytokine storm (Table 1.3). While suspecting drug as an offending agent for fever, the clinician needs to address two issues:

1. Is it really a drug fever?
2. If so, what is/are offending agents?

While finding the answer to the first question about the causality of drug fever, there may be a temporal profile, which may help in deciding if the drug is the cause of fever (Table 1.4). The review of history and/or medical records may help in knowing the exact day of onset of fever and duration of fever and its relation to drug introduction, which may help in identifying the cause of fever.

Table 1.3 Mechanism of drug fever

Mechanism	Examples
Increasing heat production	Thyroxine
Decreasing heat dissipation	Inotropes/vasopressor
Altering thermoregulatory mechanism	Phenothiazine
Inducing cytokine storm	Immuno-modulators
Pyrogenic contaminants	Amphotericin-B, bleomycin
Hypersensitivity	Carbamazepine, heparin, antimicrobials
Idiosyncratic reaction	Haloperidol

Table 1.4 Temporal association of drug and development of fever

Drug	Median (days)
Antibiotics	6
Cardiovascular	10
CNS	16
Antineoplastic agent	0.5

Table 1.5 Medicines associated with drug fever

Most common	Barbiturates, phenytoin, antihistaminic, methyldopa, penicillin, salicylates, sulfonamides, amphotericin-B, procainamide, bleomycin
Less common	Isoniazid, PAS, Streptomycin, rifampicin, propylthiouracil, streptokinase, vancomycin, nitrofurantoin, allopurinol, cephalosporin, hydralazine, azathioprine
Least common	Insulins, tetracycline, digitalis, chloramphenicol

The second question is little difficult to answer as there is a long list of medicines which may cause fever and often patients are receiving different class of drugs in both inpatient and outpatient settings. The Table 1.5 lists the most common culprit drugs involved in drug fever. The astute clinician needs to use his knowledge and keep high index of suspicion in case no other cause is apparent and one of the mentioned drug is being used in ICU. We should remember any drug may cause fever, there has been rare case reports of dexmedetomidine and pantoprazole causing fever.

1.6.2 Connective Tissue Disease (CTD)

The CTD/vasculitis as an etiology in ICU patient is difficult to consider at first place as it does not develop acutely. There may be a coexisting undiagnosed CTD or a diagnosed patient with acute complication. Both types of patients pose different clinical problem in diagnosis and management (Table 1.6). The common CTD's to be considered are RA, SLE, scleroderma, antiphospholipid syndrome, vasculitis, and dermatomyositis in decreasing order of prevalence.

Table 1.6 Issues in diagnosis and management of CTD in ICU

Clinical status	Probable outcome
Undiagnosed CTD	Delay in treatment Unexplained/early multi organ failure Rapid downhill course Increased morbidity/mortality 20% are antibody negative
Diagnosed CTD	Mortality is high Difficult to differentiate between inflammatory v/s infection as a primary insult Overlap syndrome often coexists

A peripheral smear suggesting rouleaux formation along with urinalyses showing dysmorphic RBC's (glomerulonephritis) points towards an ongoing immune insult and it should be further probed. Low complements level C3/C4 and CH50 may help to diagnosis of SLE activity. When suspecting CTD, a revision of history, medical records, treatment, and interview with relatives/friends may give you a valuable clue towards diagnosis.

1.7 Laboratory Investigation

1.7.1 Blood Culture

The growth of suspected organism along with sensitivity profile is still gold standard for selection/revision of antimicrobials therapy and antibiotic stewardship. The rapidity of MDR bugs development and paucity of newer antibiotics make situation very complex, leaving very little room to maneuver.

The following points should be remembered for blood culture sampling:

1. Multiple samples with aseptic precautions (at least 3–4 in 24 h) is must for detection/microbial growth.
2. Single sample is not recommended except for neonatal patients.
3. There is no difference of growth between arterial and venous samples.
4. Use different sites for each sample and at least 10–20 ml blood sample to be collected in blood culture bottle or BACTEC.
5. If intravascular device is in place, use separate site to obtain blood.
6. Do not use multiple port of same device.

1.7.2 Serum Procalcitonin (PCT)

The serum procalcitonin is a promising, cheap, and simple blood test to distinguish bacterial infection from other causes of infection or inflammation. PCT can be

positive in many non-infectious etiologies, especially in severe physiologic stresses (e.g., surgery, major trauma, burns, hemodialysis, multi organ failure). PCT values should always be interpreted carefully in light of history, clinical examination findings and microbiological assessment. The PCT test has following characteristics:

1. Reporting time <2 h.
2. Average sensitivity and specificity is 80–100%
3. Detectable within 2–4 h after stimulus (infection/inflammation)
4. Peaks by 12–24 h
5. Decline (half-life) 24–36 h.
6. Parallel increase with inflammation.
7. A declining trend is suggestive of resolving infection/inflammation.

1.7.3 Syndromic Testing

Rapid multiplex PCR based molecular diagnostic platforms have been developed which can screen for a wide variety of pathogens with a short turn around time. High cost remains a major bottleneck preventing the widespread use of such platforms.

1.7.4 Urine Culture

Urinary infections, especially urinary catheter infection is a major source of fever in ICU patients. Early morning mid-stream urine sample is best in a self-voiding patient. In a catheterized patient urine should be collected from Foley's catheter port and transported immediately or at least within 2 h of sample collection for optimum results.

1.8 Radiologic Investigations

Chest Radiograph Most common radiological investigation to order as it gives information about appearance of a new pulmonary lesion or worsening of the existing one. Respiratory system being the portal of entry second to genitourinary system and therefore more likely to get infected.

CT Scan Though it is not done routinely required in all patients, it may have a role in specific subset of patients especially in ICU as it provides very important information about diagnosis of pulmonary embolism and mediastinal adenopathy which is otherwise difficult to diagnose on chest radiograph. It also helps to differentiate between new or worsening lung pathology. Regarding abdomen, it is much more sensitive in detecting hepatobiliary infection/inflammation, Psoas hematoma/abscess, pancreatic necrosis, adenopathy, and retro-peritoneal collection then ultrasound.

MRI The MRI of brain becomes essential in evaluating CNS infections specially meningoencephalitis and posterior fossa lesions.

1.9 Approach to Patient with Fever in ICU

A thorough medical history and complete review of records followed by complete physical examination is paramount in localizing and identifying the cause of fever in ICU. Multiple blood culture is the only mandatory diagnostics test in patient with new onset fever in ICU as clinical examination alone cannot identify cause of fever in many critically ill patients because of low sensitivity. Further evaluation should be done in a systematic manner to find the cause of fever.

The systematic approach to patient with fever in critically illness in intensive care unit involves integration of following seven points:

1. Medical history and review of records.
2. Clinical examination.
3. Interpretation of investigative data.
4. Any chronic predisposing condition.
5. Acute condition leading to ICU admission.
6. Magnitude of fever.
7. Any recent invasive procedure.

1. Medical History and Review of Records The complete medical history should be taken from the patient or from attendant depending upon circumstances and patient's sensorium. The medical records of recent treatment, travel, or medication should be noted and confirmed from previous hospital records or prescription. The importance of good medical history in making a diagnosis cannot be ignored in ICU patients.

2. Clinical Examination The patient needs to be thoroughly re-examined from head to toe, many a times the clues lie right there or developed recently before patient being shifted to ICU from general ward. The suggested search for infectious source should start with focused examination, which should include any evidence of: abscess, localized collection, thrombophlebitis, deep vein thrombosis, cellulitis, pressure ulcers/bed sores, indwelling catheter or catheter site infections. Although its well-known that in many ICU patient focus of infection could not be find even after complete thorough examination, thus bringing the role of blood culture and laboratory investigations.

3. Interpretation of Data Any patient with fever undergoes a battery of test to ascertain the cause. The test ordered are blood culture, urine culture, chest radiograph, and examination of other relevant body fluids in descending order. However, it is the interpretation of laboratory and radiological data that differentiate between infectious from a non-infectious cause. Therefore, for interpretation of laboratory data the following points should be considered:

1. There are marked overlap of organism between normal and pathogenic, especially gastrointestinal tract, and genital systems.
2. For blood culture, compare the number of samples drawn with positive growth and organism grown.
3. For suspected UTI, the urinalyses should show >10 WBC/hpf and CFU > 10^5/ml unless the sample is collected by special procedure (i.e., suprapubic aspiration).

4. Any Predisposing Condition Patient with pancytopenia due to leukemia, post-chemotherapy is more prone to develop febrile neutropenia leading to gram negative sepsis or even fungal infection. Similarly, immunocompromised patients with HIV may have atypical infection from pneumocystis or mycobacterium. Knowing of predisposing condition will help in further investigation and arriving at diagnosis.

5. Acute Condition Leading to ICU Admission Rarely patients with congestive heart failure, ARDS, traumatic brain injury, Addison's crisis, seizure or pulmonary embolism may present with fever due to primary illness only, instead of any infection.

6. Magnitude of Fever Body temperature above 41 °C is commonly seen in non-infectious causes, especially hyperthermia. This hyperthermia syndrome does not respond with antipyretics and is secondary to dysfunction of thermoregulatory centers in brain. Fever between 38.9 °C (102 °F) and 41 °C (105.8 °F) usually considered to be secondary to infectious source.

7. Recent Invasive Procedure Any diagnostic or therapeutic procedures done recently can be source or portal of infection in ICU patients. The fever can be due surgical site infection (>48 h of surgery) or benign post-operative fever. Common ICU procedures like CVP line insertion, urinary catheterization, tracheal intubation, arterial line can lead to fever in ICU patients.

1.10 Management

The management of fever in ICU is very challenging for intensivist. First and foremost, he has to investigate and decide if the cause of fever is infectious or non-infectious and then further proceed. The three most crucial decision an ICU specialist has to take in a febrile patient is to decide if patient should be started on empirical antibiotics (especially if the focus of fever is not found), secondly to remove or not to remove an indwelling catheter, and lastly if the patient should be treated with antipyretics or not.

1.10.1 Empiric Antibiotic Therapy for Suspected Infection in a Febrile Patient

If an infectious cause of fever is suspected in ICU patients, broad spectrum antibiotics should be started as soon as possible after taking appropriate cultures. There are studies which suggest that timely appropriate antibiotics in sepsis patients lead to reduced ICU stay and reduced mortality. Empirical antibiotics should be started on priority in patients in shock, neutropenia, and suspected infected ventricular assist device. Patients who are stable and whose temperature is below 102^0F should be further evaluated before starting antibiotics therapy.

1.10.2 Removal of Catheter in Febrile Patient

Infected central venous catheter should be removed immediately in a catheter related blood stream infection (CRB). The consideration should be given to severity of illness, age of indwelling catheter, probability of catheter being infective source in an unproven case of blood stream infection.

1.10.3 Antipyretics or Cooling Therapy for Fever

There is conflicting data for treatment of fever with antipyretics or external cooling in ICU patients and therefore it should not be routinely treated especially in septic patients. Exceptions to it are patients having very high core temperature (>41 °C/106 °F), patients with acute stroke or traumatic brain injury (raised ICP), limited cardio-respiratory reserve (post cardiac arrest), as in these situations higher temperature may lead to tissue injuries. Patient having significant discomfort due to fever and pregnant female may also be treated with antipyretics as there is chances of fetal malformations. If decision is taken for treating fever, then it should be ideally treated with oral/intravenous acetaminophen.

1.11 Conclusion

Fever is seen in 2/3rd of ICU admission in some point of their care. It is recommended to follow a clinically driven, systematic, cost-effective approach for evaluation of febrile ICU patients. Empirical antibiotics should only be started as soon as possible in patients who are very sick, in shock, neutropenic, or having suspected infected ventricular assist device. As there is no robust data to suggest any benefit in treating fever with antipyretics, therefore, the lowering of temperature is only recommended in patients with acute brain injury, hyperthermia, and in patients with reduced cardiorespiratory reserve to prevent excessive tissue injury and mortality.

Suggested Readings

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Clinical Approach to Sepsis

2

Ankit Mittal and Manish Soneja

2.1 Introduction and Definition

Sepsis is a clinical syndrome resulting from dysregulated physiologic, pathologic and biochemical response to an infection. It not only results from an abnormal activation of the immune system but also due to its paralysis. It can lead to multi-organ dysfunction and subsequently death. Therefore, it warrants urgent recognition and appropriate management.

The definition of sepsis has evolved over decades, first described in 1992 in conjunction with severe inflammatory response syndrome (SIRS). It was revised in 2001 (Sepsis-2) and the most recent revision came in 2016 with the publication of sepsis-3 consensus document. While the first and second definitions revolved around SIRS with sepsis-2 defining "sepsis", "severe sepsis" and "septic shock" as three separate entities, the latest definition has done away with the term "severe sepsis".

Sepsis-3 defines sepsis as "a life-threatening organ dysfunction caused by a dysregulated host response to infection". The latest definition has incorporated mortality indicators in the form of Sequential Organ Failure Assessment (SOFA) scoring (Table 2.1). Organ dysfunction can be objectively identified as an acute increase in SOFA score by 2 as compared to the baseline (to be taken as zero in absence of a pre-existing organ dysfunction) (Rhodes et al. 2017). For patients outside ICU, qSOFA (quick SOFA) score of 2 out of 3 was found to perform as well as SOFA and should guide physicians for intensive monitoring, escalation of therapy and transfer to a critical care unit [Components of qSOFA: altered mentation, SBP ≤100 mm of Hg and respiratory rate ≥22/min]. However, the overall sensitivity and specificity are around 60% and 72% for prediction of mortality. It also needs to be kept in mind

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Table 2.1 SOFA scoring[a]

	0	1	2	3	4
Respiratory • P/F ratio	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation • Platelets ($\times 10^3$ /ul)	≥150	<150	<100	<50	<20
Liver • Bilirubin, mg/dl	<1.2	1.2–1.9	2.0–5.9	6.0–11.9	>12
Cardiovascular [catecholamines, ug/kg/min]	MAP ≥ 70 mmHg	MAP <70 mmHg	Dopamine <5 or dobutamine (any dose)	Dopamine 5-15 or norepinephrine <0.1 or epinephrine <0.1	Dopamine >15 or norepinephrine >0.1 or epinephrine >0.1
Central nervous system • Glasgow Coma Scale (GCS)	15	13–14	10–12	6–9	<6
Renal • Creatinine, mg/dl • Urine output, ml/day	<1.2	1.2–1.9	2.0–3.4	3.5–4.9 <500	>5.0 <200

[a]Vincent et al. (1996)

that the scoring system only identifies patients at increased risk of dying due to organ dysfunction and does not tell us if it is truly due to an underlying infection. Thus, clinical judgement aided by radiological and microbiological evidences currently remain the only effective tools for identifying sepsis.

Septic shock is defined as a subset of sepsis in which underlying circulatory, cellular and metabolic abnormalities are profound enough to substantially increase mortality. The clinical criteria to identify septic shock are need for vasopressors to maintain a mean arterial pressure (MAP) of or above 65 mm of Hg and a serum lactate level above 2 mmol/L despite adequate fluid resuscitation (Box 2.1). Septic shock carries a high mortality rate of >40%.

Currently, no definition can claim to be 100% sensitive and specific for recognition of sepsis and the definition needs to be revised periodically, as our understanding of the underlying pathobiology of sepsis becomes clearer. Also, these definitions do not apply to patients with tropical infections (dengue, scrub typhus, leptospirosis, etc.) where the presentation might be similar but the pathophysiology and subsequently management will be different. Also, it is difficult to apply standard definitions and guidelines to special population (chronic liver disease, chronic kidney disease, chronic heart failure, HIV, malignancies and other

Box 2.1 Sepsis-3 Criteria for Sepsis/Septic Shock (Adapted from Singer et al. (2016))

- *Sepsis*: qSOFA ≥2 plus evidence of infection
- *Septic shock*: Sepsis plus persistent hypotension requiring administration of vasopressors to maintain a MAP>65 mmHg and a lactate >2 mmol/L despite adequate fluid resuscitation

immunocompromising conditions). In the truest sense, the guidelines are applicable only to cases of suspected bacterial infections in an otherwise healthy adult. Probably newer definitions could incorporate inclusion of new biomarkers that will improve the sensitivity and specificity of diagnostic definitions.

2.2 Epidemiology

In 2017, an estimated 48.9 million cases of sepsis were recorded worldwide with 11.0 million sepsis-related deaths. This represented around 19.7% of all global deaths. Sepsis incidence and mortality varied substantially across regions, with the highest burden in sub-Saharan Africa, Oceania, south Asia, east Asia, and southeast Asia (Rudd et al. 2020). In USA alone, an estimated 1.7 million patients are admitted with sepsis and 270,000 die annually (Rhee et al. 2019; Liu et al. 2014). The latest estimates range between 0.4/1000 and 1/1000 of the population in the USA, Europe, and the United Kingdom (Angus et al. 2001; Brun-Buisson et al. 2004; Harrison et al. 2006). A review of data on 10 million cases of sepsis over a 22-year period showed an 8% annual increase in the incidence of sepsis (Martin et al. 2003). The rise in cases may be attributed to reasons such as: increased recognition, higher population in the extremes of ages, increasing number of patients on immunosuppressive therapy, increase in the prevalence of drug resistant organisms, etc.

The impact of sepsis on mortality, length of stay and healthcare costs is huge. Mortality related to sepsis appears to be up to 140% higher and average length of stay was 75% longer compared to other causes (Epstein 2016; Products - Data Briefs 2019). Although data from the USA shows a decline in the overall mortality due to sepsis (from 28% to 18%), it is still very high (Martin et al. 2003). A retrospective cohort review from 6 US hospitals showed that sepsis was responsible for 52.8% of all admissions and was the cause of death in 34.9% cases followed by progressive cancer (16.2%) and heart failure (6.9%) (Rhee et al. 2019). Estimates also show that sepsis accounts for the majority of 30-day readmissions. Data from developing countries is almost non-existent despite being responsible for the greatest burden of the disease with worse outcomes (Adhikari et al. 2010; Black et al. 2010). A study from Brazil reported that from 2006 to 2015 the annual incidence of sepsis increased by 50.5% from 31.5/100,000 to 47.4/100,000 with an overall mortality of 46% and 64.5% in ICU admissions (Neira et al. 2018).

Incidence of sepsis is more in elderly males, non-whites and immunosuppressed individuals (including HIV/AIDS, cirrhosis, asplenia, autoimmune disease and cancer patients). Studies have also shown genetic predisposition in certain individuals as a risk factor for sepsis (for example: TLR4 polymorphism has been associated with increased susceptibility to gram negative infections, candidemia and other invasive fungal infections) (Ferwerda et al. 2007).

The most common site of infection that leads to sepsis is the lung (64% of cases), followed by the abdomen (20%), bloodstream (15%) and renal and genitourinary tracts (14%). The most common organism implicated as the cause of sepsis depends on the site of infection, source of infection (community or hospital acquired), immune status of the patient as well as the local epidemiology besides other factors. Most data sources are localized in the West or in developing countries and we need to be careful while extrapolating these results. In some regions gram-positive sepsis may predominate, whereas in other regions the trend might be shifting towards gram negatives (Chatterjee et al. 2017; Vincent et al. 2009; Karlsson et al. 2007; Dagher et al. 2015).

2.3 Pathophysiology

The normal host response to infection aims to localize and control the bacterial invasion and simultaneously initiate repair of injured tissue. The overall immune interaction is complex and beyond the scope of this chapter. Activation of phagocytic cells, as well as the generation of proinflammatory and anti-inflammatory mediators is the pivotal process. This may occur by several pathways. An important pathway is recognition and binding of pathogen-associated molecular patterns (PAMPs) of microorganisms by the pattern recognition receptors (PRRs) on the surface of host immune cells. This in turn activates a cascade that leads to release of inflammatory cytokines (IL-1, IL-6, TNF-α). It also leads to recruitment of more neutrophils, macrophages, lymphocytes and sets in a hyperinflammatory state (Dunn 1991; Takeuchi and Akira 2010). This hyperinflammatory state is kept in check by the anti-inflammatory pathways. Disruption of this homeostasis in favour of hyperinflammatory state leads to the so-called cytokine-storm and is responsible for tissue damage and organ dysfunction in early sepsis. It also leads to endothelial injury with capillary leaks that lead to third spacing of fluids and decreases the effective intravascular volume leading to hypoperfusion (Takeuchi and Akira 2010; Schulte et al. 2013). Besides, reactive oxygen species produced are directly toxic to the mitochondria which in turn inhibits the aerobic cellular respiration and ATP generation along with formation of lactic acid (Brealey et al. 2002; Singer 2014). After this initial phase of immune-activation, the patient enters a state of immune-paralysis although little is known about the timeline of this progression. It mostly occurs due to T-cell exhaustion (increased apoptosis, decreased proliferation and cytotoxicity) as well as myeloid cell dysfunction (decreased antigen presentation, decreased releases of cytokines). These are possibly mediated by an upregulation in immune check point inhibitors (programmed death-1 (PD-1), programmed death ligand-1 (PD-L1), cytotoxic T lymphocyte antigen-4 (CTLA-4), T-cell membrane protein-3 (TIM-3), etc.) (Patil et al. 2017). Further research is needed to possibly

measure the onset and level of immunosuppression in these patients. Furthering our knowledge on pathophysiology of sepsis can help us to design more appropriate and precise interventions.

2.4 Clinical Presentation

The typical presentation of a patient with sepsis is with fever, tachycardia, and leukocytosis, and subsequently may develop features of poor perfusion and organ dysfunction (respiratory distress, decreased urine output, poor sensorium, jaundice, hypotension, etc.). Patients may also develop disseminated intravascular coagulation and present with bleeding manifestations. In the early phases, the skin might be warm and flushed. However, as the shock worsens, the skin may become cold and clammy with decreased capillary refill, cyanosis, or mottling.

Effective history taking (including assessment of co-morbidities, immune status, previous hospitalization, etc.) and a thorough clinical examination are mandatory and help in suspecting and localizing the source of infection as well as to guide selection of effective antimicrobials. Examination should also focus on identifying removable sources of sepsis (for example, an abscess, infected devices, etc.) when present.

Liaising with the surgical team will be of utmost importance in such cases. Assessment of scores at baseline (SOFA, APACHE, SAPS II, NEW, etc.) although cumbersome, can help in effective prognostication (Le Gall et al. 1993; Huang et al. 2017).

It is important to note that such presentation is not specific to sepsis and conditions like viral hemorrhagic fevers, tropical infections, pancreatitis, thromboembolism, autoimmune diseases, etc. may present similarly.

2.5 Investigations

The objective of ordering laboratory investigations is diagnostic as well as prognostic.

As dictated in SOFA scoring, investigations should be ordered to assess organ dysfunction. Complete blood count, liver and renal function tests, blood gas analysis should be ordered as a routine at baseline. Blood cultures are perhaps the most important investigation in cases of sepsis. Sterile collection technique, right timing (before administration of antibiotics), and appropriate volume (two or more sets, with at least 10 ml blood in each bottle) significantly affects the yield. Automated systems are largely taking over conventional blood culture processing techniques. Molecular diagnostics where available can help in rapid identification of organisms. Beside this, based on history and examination, further diagnostic tests should be ordered (for example, urine microscopy and culture, sputum microscopy and culture, etc.). It is important to follow the set protocols while obtaining samples for microbiological investigations to avoid contamination and false negative reports.

Common lab abnormalities that may be noted (but are not specific) in cases of sepsis include neutrophilic leukocytosis with toxic granulation, thrombocytopenia, deranged renal and liver functions as well as deranged coagulation profile. Increase

in serum lactate (> 2mmol/L) is a marker of poor end-organ perfusion. Elevated biomarkers e.g. CRP, procalcitonin, etc. are also common. Hypoxemia could be subsequent to pneumonia and/or acute respiratory distress syndrome (ARDS).

Focused imaging studies based on clinical assessment are required in most cases to help in early localization of source.

2.6 Culture Negative Sepsis (CNS)

CNS remains a major problem in the management of sepsis as a large number of cases fall into this group (28–49%), more so in the developing countries and optimizing antimicrobial treatment in this group remains a challenge (Brun-Buisson et al. 2004; Martin et al. 2003, 2009; Blanco et al. 2008). Therefore, a large number of cases are culture negative, more so in the developing countries and optimizing antimicrobial treatment in this group remains a challenge. Causes could be administration of antibiotics prior to collection of cultures, improper collection techniques, poor laboratory support or patients being misdiagnosed as sepsis. Also, viral and fungal sepsis especially in immunocompromised patients or infections by fastidious bacteria/ atypical organisms (scrub typhus, leptospirosis, etc.) might lead to CNS. It eventually leads to increased usage of broad-spectrum antibiotics for longer duration as de-escalation becomes difficult. This in turn contributes to emergence of antibiotic resistance over time and also more incidences of drug related adverse events and other hospital acquired infections like *C. difficile*, etc. (Johnson et al. 2011; Eze et al. 2017).

Study by Gupta et al. tried to look at the nationwide trend and outcome in CNS in USA. Out of more than 6 million admissions with sepsis, 47.1% were identified as CNS with the incidence rising over the years. CNS patients had more co-morbidities, acute organ dysfunctions and in-hospital mortality (34.6% vs. 22.7%; $p < 0.001$). Also, CNS was identified as an independent risk factor for mortality conferring a 75% excess risk of death compared to culture positive sepsis (Gupta et al. 2016). The data from developing countries are possibly worse with higher incidence of CNS and higher mortality.

However, there are other studies by Phua et al. and Kethireddy et al. that did not demonstrate any significant difference in mortality between the CNS and the CPS group (Phua et al. 2013; Kethireddy et al. 2018). Therefore, it is an area where more research and more epidemiological studies are required, especially from the developing countries.

2.7 Biomarkers in Sepsis

The previously used SIRS criteria and the currently used SOFA scoring can misclassify organ dysfunction due to non-infectious causes as sepsis. This is a major concern as it can lead to inappropriate use of antibiotics which in turn can lead to increase in drug resistance. It will also cause a delay in diagnosis which can

adversely affect patient outcomes. Also, viral and fungal sepsis need to be differentiated from bacterial causes as the management strategies would differ. Therefore, it is highly desirable to have a marker that can reliably differentiate infectious from non-infectious causes as well as bacterial from viral/fungal causes of sepsis. Several biomarkers have been tried and tested, but none of them has been found to perform reliably. An ideal sepsis biomarker would diagnose, stage the disease as well as indicate the prognosis and clinical response to treatment (Biomarkers Definitions Working Group 2001).

Some of the commonly used biomarkers are C-reactive protein (CRP), procalcitonin (PCT), presepsin, CD64, soluble-urokinase-type-plasminogen-activator-receptor (suPAR), soluble triggering receptor expressed on myeloid cells 1(sTREM-1). A novel assay, Septicyte LAB gene expression assay which utilizes transcriptomics has shown great promise (Verboom et al. 2019).

a. *Procalcitonin*: It is one of the most popular and commonly used biomarkers used to initiate/escalate/de-escalate antibiotics but it should never override clinical judgement. However, recent systematic reviews have challenged the use of PCT in sepsis. In a meta-analysis of 12 studies with 2408 patients with community acquired pneumonia (CAP), the sensitivity and specificity of serum procalcitonin were 0.55 (95% CI = 0.37, 0.71; I2 = 95.5%) and 0.76 (95% CI = 0.62, 0.86; I2 = 94.1%), respectively. Also, it was found to be unreliable in differentiating viral from bacterial sepsis (Kamat et al. 2020). Moreover, PCT can be raised in severe physiologic stress conditions, malignancy, renal disease, etc. PCT based algorithm may, however, be used for de-escalation of antibiotic therapy. This approach can result in decreased antibiotic usage (Pepper 2019). Initiation of antibiotics should mostly be on clinical judgement and should not be guided by PCT values alone. When used for guiding early discontinuation, values may be attained at every 48 h and antibiotics may be discontinued if values are <0.5 ng/ml or a decrease by >80% (when initial levels were >5ng/ml).
b. *Presepsin*: It is a soluble CD14 expressed on monocytes and macrophages and is released during sepsis. Advantage over PCT or IL-6 is that it rises earlier in sepsis (Shozushima et al. 2011). However, a recent meta-analysis of 8 studies found that presepsin was not a good test for diagnosis as well as prognosis when used alone (Zhang et al. 2015).
c. *CD64, suPAR and sTREM-1*: Evidence is lacking to recommend the routine use of these biomarkers although they do hold promise. Although most studies cannot be extrapolated to today's practice because of heterogeneity in the definition of sepsis that was used in these studies. For example, a study found that suPAR was an independent predictor of 30-day mortality in ICU patients as compared to lactate and PCT (Casagranda et al. 2015). Application of sTREM-1 could be in its measurement in body fluids where it is generally found to be elevated in cases of infections (Cao et al. 2017). All such biomarkers need more robust evaluation which is now possible with availability of a universally acceptable definition of sepsis. Most of these tests have limited application due to their poor sensitivity, specificity and cost.

d. *Septicyte LAB gene expression assay*: The test generates a SeptiScore™ based on the results of quantitative real time PCR that targets CEACAM4, LAMP1, PLAC8 and PLA2G7 in whole blood. Scores could range from 1 to 10 with a higher score indicating sepsis. This was recently approved by the US-FDA (Verboom et al. 2019).

2.8 Diagnosis

There is no single symptom or sign or investigation that can reliably diagnose sepsis. It is usually an diagnosed based on the composite of history, examination and relevant investigations (laboratory, microbiological and radiological).

2.9 Approach to Management

Recognizing sepsis early is important, but recognizing sepsis mimickers (pancreatitis, thromboembolism, vasculitis, drug reactions (neuroleptic malignant syndrome, DRESS) and autoimmune and neoplastic processes such as lymphoma and hemophagocytic lymphohistiocytosis) is equally important. Also, physicians in tropical countries should be aware of conditions like viral haemorrhagic fevers, severe malaria, scrub typhus, leptospirosis, etc. which might be common in their setting and mimic bacterial sepsis.

A change in SOFA by ≥2 is associated with 10% mortality and septic shock has a mortality of >40% (Martin et al. 2003). Once a patient with sepsis/suspected sepsis is identified, the management should be initiated immediately. The ED team should be able to triage such patients as soon as possible. A dedicated team should be formed comprising of ED physicians, critical care specialists, infectious diseases specialists and trained nursing staff. All efforts should be made to implement the "1-h Bundle" in principle which includes measuring lactate levels, taking blood cultures prior to initiation of antibiotics, administering broad-spectrum antibiotics and initiation of fluid resuscitation (Levy et al. 2018) (Box 2.2). In resource limited, high burden settings it would be impractical to expect implementation of the bundle. A more pragmatic approach would be to do things "as

Box 2.2 Surviving Sepsis Campaign 1-h Bundle (Levy et al. 2018)

- Measure lactate level (follow serial measurements if initial level >2 mmol/L)
- Obtain blood cultures prior to administering antibiotics
- Administer broad-spectrum antibiotics
- "Begin" rapid administration of 30 mL/kg of crystalloid for hypotension or lactate ≥4 mmol/L
- Start vasopressors if patient is hypotensive during or after fluid resuscitation to maintain a MAP _65 mmHg

soon as possible". However, certain things (fluid resuscitation, antibiotic administration) are undebatable and should be instituted within the given time frame. Early and effective antimicrobial therapy is the corner-stone of management and should not be delayed by more than 45 min to 1 h in case blood cultures could not be drawn (Ferrer et al. 2014). A study assessed the door to antibiotic timing in sepsis and found that delay in administering antibiotics was associated with an increase in long-term mortality (Peltan et al. 2019). A practical approach to patient that comes to the emergency has been summarized in the Figs. 2.1 and 2.2. Early goal directed therapy (EGDT) which was proposed as the ideal approach has now been found to be ineffective. A meta-analysis of the three major trials on EGDT (ProCESS, ARISE and ProMISe) concluded that EGDT did not result in better

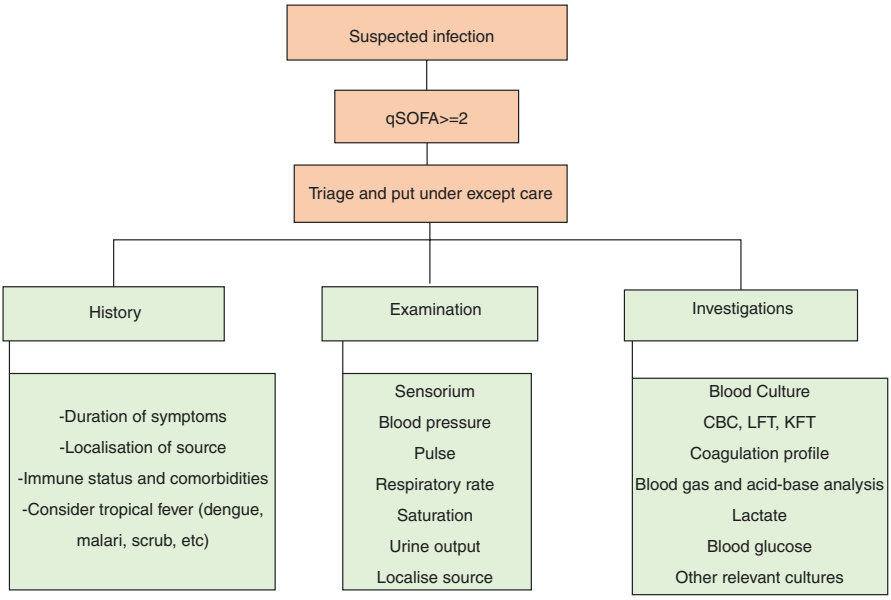

Fig. 2.1 Approach to a case of sepsis

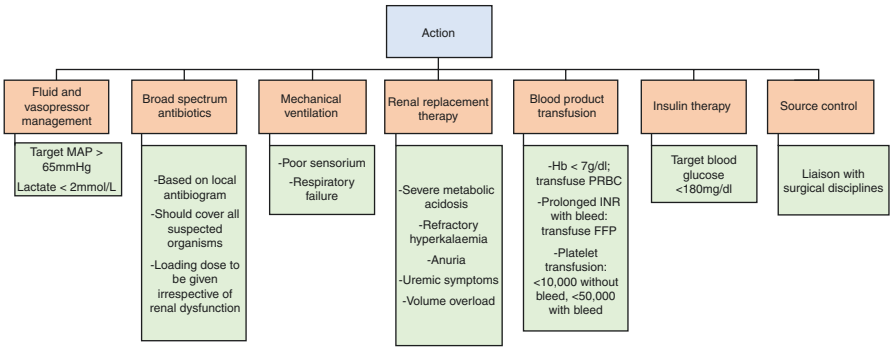

Fig. 2.2 Overview of management of sepsis

outcomes than usual care. It was also associated with higher cost of care (Investigators et al. 2017).

1. *Antimicrobial therapy*: "Hit hard and hit fast" is the thumb rule. Sick patient should receive empirical broad-spectrum antibiotics that should include all suspected organisms. All efforts should be made to collect blood and/or other relevant cultures before initiation of antibiotics. The culture positivity directly depends on the volume of blood culture drawn and therefore large volume blood cultures (at least two sets, 10ml in each bottle) should be taken and processed in automated systems.

   There can practically be no guidelines with respect to choice of antibiotics that would apply to all Table 2.2 mentions the various risk factors for suspecting an infection with MDR-GNBs, MRSA, VRE or Candida. Also, local epidemiology of prevalent microorganisms with their susceptibility profile should guide the choice of antibiotics and each ED/ICU should have their antibiotic policies protocolized. This might be a major problem in the developing countries as very little epidemiological data has been generated till now. Emergence of MRSA, ESBL and carbapenemase producing organisms pose a major threat to effective antibiotic therapy.

   The pharmacokinetics and pharmacodynamics need to be kept in mind when prescribing antibiotics for any particular condition, keeping in mind the organ dysfunction. Most patients are at a risk of under-dosing of antibiotics which may be detrimental (Smith et al. 2012). Also, in patients with severe disease/ shock, the absorption of drugs from the gut will be questionable and parenteral therapy should be the preferred. Therapeutic drug monitoring (e.g. vancomycin, β-lactams) should be done when possible (Veiga and Paiva 2018; Wong et al. 2018).

   Once culture reports are available and compatible with the clinical condition, the antimicrobial therapy should be shifted to the narrowest possible spectrum. However, many a times, the in-vitro and in-vivo sensitivities may not correlate,

Table 2.2 Risk factors for select organisms[a]

MDR GNB	*MRSA*	*VRE*	*Candida*
• IV antibiotics within 90 days • Five or more days of hospitalization prior to onset • Requiring acute renal replacement therapy • Septic shock • Colonization with MDROs	• Colonization with MDROs • Recent MRSA infection • Known MRSA colonization • Purulence or abscess of the skin or IV access site • Severe rapidly progressive necrotizing pneumonia	• Liver transplant • Known colonization • Prolonged use of broad-spectrum antibiotics • Profound immunosuppression	• Central venous catheter • Broad-spectrum antibiotics • Plus, one of the following – Parenteral nutrition – Dialysis – Recent abdominal surgery – Necrotizing pancreatitis – Immunosuppressive agents

[a]Adapted from Derensinski and Stan. "Severe Sepsis and Septic Shock Antibiotic Guide". Stanford Antimicrobial Safety and Sustainability Program. Stanford Health. May 2017

or the sepsis may not be attributable to a single organism in which case clinical sense should prevail above everything else. A duration of 7–10 days is considered adequate for most infections but need to be individualized depending on the causative organism and disease severity (Rhodes et al. 2017). It is advisable to seek infectious diseases consultation while optimizing regimen.

2. *Fluid therapy and measuring responsiveness*: Prompt initiation of fluid resuscitation in severe disease is of paramount importance. The current recommendation is to administer 20–30 ml/kg intravenous fluid (preferably balanced crystalloids), to be initiated within 1 h of presentation and completed within 3 h. Fluids should be administered in 250–500 ml rapid boluses and patients should be monitored for clinical and hemodynamic response. Whereas some patients may require more fluids, they should be carefully monitored for development of features of fluid overload. It is imperative to note that hypotension in some cases will not respond despite fluid resuscitation and may lead to a state of fluid overload which is independently associated with poor clinical outcomes in patients with sepsis. The treating physician will need to consider the risk versus benefit of continuing fluid resuscitation versus initiation of vasopressors and inotropes since hypotension and hypoperfusion are not only the result of capillary leakage and third spacing, but also due to the loss of vascular tone and decrease in peripheral resistance.

   Recommendations for fluid therapy are mostly drawn from studies done in developed countries. In contrast, some studies from countries with resource limited setting have shown poor outcomes with protocol driven therapies and mandate caution while administering fluid in sepsis where monitoring is not possible (Maitland et al 2011; Andrews et al. 2014). There is still uncertainty surrounding a liberal versus restrictive fluid resuscitation strategy since no study has till date decisively answered this question. Assessment of fluid responsiveness using certain dynamic variables (pulse pressure variation, stroke volume variation, inferior vena cava collapsibility, etc.) may guide us in administering fluids but these tests themselves suffer from poor sensitivity and specificity as well as marked inter-observer variations. Fluid therapy may also be guided by monitoring the lactate clearance. It acts as a surrogate marker of patient's response to therapy. However, hyperlactatemia is not only a consequence of decreased perfusion, but also of decreased oxygen utilization by the tissues.

   After initial resuscitation, fluid therapy should be directed to maintain intravascular volume and replace ongoing fluid losses. While guidelines cater to the majority of patients, patients with severe disease might require an individualized approach.

   Choice of fluid: The optimal fluid has always been a matter of debate. Most guidelines recommend crystalloids as the initial fluid of choice. Amongst crystalloids, balanced solutions may be preferred. The SMART trial done in critically ill patients compared saline with balanced crystalloids (Ringer's lactate or Plasma-Lyte A) and found that saline usage was associated with a higher rate of composite outcome of death and persistent renal dysfunction (Semler et al. 2018). In another trial, although there was no difference in mortality, the incidence of kidney injury was found to be lower with balanced crystalloids (Self et al. 2018). Colloids are not the preferred agent for initial resuscitation but they

may be used when the requirement for crystalloids is high. However, currently evidence to support the use of colloids is lacking (Caironi et al. 2014; Perel et al. 2019).

3. *Vasopressors*: In addition to capillary leakage, sepsis leads to decreased adrenergic responsiveness and a pathologic imbalance between local vasoconstrictor and vasodilatory mediators (NO, endothelin, thromboxane A2, etc.). This leads to blood flow heterogeneity within organs consequently leading to hypoperfusion and organ damage. Although classically vasopressors are introduced when MAP remains <65 mmHg despite adequate fluid resuscitation, it is important to note that in cases of severe hypotension, early initiation of vasopressor therapy might be necessary even if the hypovolemia has not been corrected. Results of the CENSER trial showed a significantly higher shock control rate (defined as achievement of mean arterial blood pressure >65 mmHg, with urine flow >0.5 mL/kg/h for 2 consecutive hours, or decreased serum lactate >10% from baseline) than standard treatment in the early vasopressor group (76.1% vs 48.4%) (Permpikul et al. 2019).

   A MAP of 65–70 mmHg is considered adequate to maintain tissue perfusion and higher MAPs should not be targeted as it would translate to higher fluid and vasopressor load which could be detrimental.

   Regarding the choice of vasopressors, the SSC guidelines recommend norepinephrine as the first drug of choice which can be supplemented by epinephrine and vasopressin. Also, there are no clear recommendations on when to add a second vasopressor or in other words when should one think to spare norepinephrine. Norepinephrine has a strong alpha-adrenergic selective action, whereas epinephrine has a non-selective alpha + beta adrenergic action. Epinephrine at higher doses can cause myocardial ischemia, hyperglycaemia, hyperlactatemia and arrhythmias. Dopamine is a potent vasopressor only at higher doses (>10 mcg/kg/min) and at that high a dose the chance of tachyarrhythmias is very high. It may be used in patients with absolute or relative bradycardia. Dopamine (at lower doses) should not be used as a renal protective agent.

   Vasopressin acts via the V1 receptors to cause vasoconstriction. A low-dose vasopressin can help in reducing the doses of norepinephrine. It can also help to restore blood pressure in patients with limited response to norepinephrine without much adverse effects. The salient features of each vasopressor have been summarized in Table 2.3. Angiotensin II, selepressin and nitric acid (NO) inhibitors are upcoming attractive options.

   Inotropes: Dobutamine may be added to a vasopressor in the presence of myocardial dysfunction or when hypoperfusion does not revert despite achieving adequate intravascular volume and adequate MAP. However, evidence supporting the role of inotropes is weak.

4. *Steroids in sepsis*: Currently, steroids are recommended only in fluid non-responsive shock with persistent inotrope requirement (Rhodes et al. 2017; Pastores et al. 2018; Annane et al. 2017; Nishida et al. 2018). Routine use of steroids in septic shock is not recommended.

   The two major trials on corticosteroid usage are the ADRENAL trial and the APROCCHSS (Venkatesh et al. 2018; Annane et al. 2018). The ADRENAL trial did not find any difference in the 90 days mortality between the hydrocortisone

Table 2.3 Summary of commonly used vasopressors

	Dose	Receptor	Major effect
Norepinephrine	0.01–3 mcg/kg/min	α >> β	Vasoconstriction
Epinephrine	0.01–0.7 mcg/kg/min	α & β non-selective	Vasoconstriction *Note*: At higher doses Decreased splanchnic blood flow, hyperglycemia, hyperlactatemia, tachyarrhythmias
Dopamine	2–20 mcg/kg/min Predominant α and β action is seen at doses >10 mcg/kg/min	DA > *β* > *α*	Vasoconstriction *Note*: Can cause tachyarrhythmias at doses >10 mcg/kg/min
Vasopressin	0.03 U/min (addition as a norepinephrine sparing)	V1	Vasoconstriction *Note*: While discontinuing, it should be slowly tapered

and the placebo group although there was a more rapid reversal of shock with lesser duration of ICU stay. On the other hand, APROCCHSS showed that hydrocortisone plus fludrocortisone arm had decreased 90-day mortality but there was an increase in risk of hyperglycaemia and viral infections.

The optimal steroid drug, its dosing, and duration are still not clear. The most commonly used drug is hydrocortisone at doses on 200–300 mg/day in divided doses or infusion. Usually the steroids are administered for 7–14 days (Sprung et al. 2008). Steroids may however increase the risk of neuromuscular weakness (Wilcox 2017).

5. *Other supportive management and goals*:
   a. *Respiratory support*: Patients with septic shock might have poor sensorium, severe respiratory distress (due to metabolic acidosis, ARDS, etc.) and might require respiratory support in the form of mechanical ventilation (MV), invasive as well as non-invasive. Detailed discussion of managing a patient on MV is beyond the scope of this chapter.
   b. *Glycaemic control*: A target blood sugar level of ≤180 mg/dl is desirable (Rhodes et al. 2017). Strict glycaemic control may not be necessary and accidental hypoglycaemia can be harmful. Short acting insulin (as intermittent boluses or infusion) is usually the drug of choice. Longer acting insulins might be detrimental especially in cases with renal dysfunction.
   c. *Renal replacement therapy*: Patients with acute renal failure/severe metabolic acidosis/life threatening dyselectrolytemia require renal replacement therapy. In cases with severe metabolic and electrolyte disturbances, one should be cautious about the development of Dialysis Disequilibrium Syndrome (DDS) post-dialysis (Zepeda-Orozco and Quigley 2012).
   d. *Transfusion of blood and blood products*: The target haemoglobin should be somewhere around 7–8 g/dl in most conditions (Holst et al. 2014). Patients with sepsis might bleed due to disseminated intravascular coagulation (DIC) or thrombocytopenia or platelet dysfunction. Monitoring PT/aPTT/INR and platelet counts is important. In cases with severe thrombocytopenia (<10,000/mm^3) or any thrombocytopenia with bleed platelets should be transfused. In presence of DIC with bleeding, fresh frozen plasma should be transfused to

supplement the coagulation factors. Newer modalities like thromboelastography (TEG) might find application in such patients in future (Howley et al. 2018; Haase et al. 2015).

e. *Bundle approach for caring of a critically ill patient*: Various other measures that are important for the care of a critically ill patient could be observed by following a bundle approach. Things like care of the central line, urinary catheter, intubation tubing are quintessential to prevent hospital acquired infections which in itself are catastrophic. Supplementing with adequate macro- and micronutrients (enteral and/or parenteral), stress ulcer prophylaxis, care of the bowel, etc. are also important. ICUs can make bundles or checklists that can ensure patients are not devoid of the right care (Golzari and Mahmoodpoor 2014; Horner and Bellamy 2012).

f. *Nutritional support*: Sepsis is characterized by high catabolism and lean body mass loss which might persist for months to years. Timely and adequate nutritional support (to correct micronutrient/vitamin deficiencies, deliver adequate protein (~1.0 g/kg/d) and moderated non-protein calories (~15 kcal/kg/d) is of paramount importance. Feeding by enteral route should be initiated within 24–48 h after the diagnosis of sepsis in hemodynamically stable patients. Underfeeding and malnutrition is associated with longer hospital stay and higher mortality (Wischmeyer 2018).

6. *Secondary infections in sepsis*: Patients admitted with sepsis are more prone to develop secondary infections/hospital acquired infections with multidrug resistant organisms, fungi and reactivation of latent viruses. This could be because of multiple factors like exposure to broad-spectrum antibiotics, poor infection control practices, colonization with MDR organisms during prolonged ICU stay and immune-paralysis. A 8-year retrospective study from China showed that the incidence of secondary infections in patients admitted with sepsis was around 39% and the most common organisms were MDR-GNB and Candida albicans with a significantly higher mortality (Zhao et al. 2016). Therefore, in patients with sepsis with a "double sickening" all such causes should be kept in mind and should be evaluated thoroughly for a secondary infection. Antibiotic therapy would depend on the local epidemiology and antibiogram when culture reports are inconclusive.
7. *Adjunctive therapy and future perspectives*:
   a. *Vitamin C, Thiamine and Hydrocortisone*: Marik et al. proposed that a cocktail of vitamin C, thiamine, and hydrocortisone when given to patients with sepsis, significantly reduced the mortality (Marik et al. 2017). The therapy targets the non-oxygen delivery dependent mechanisms of organ dysfunction in sepsis unlike the standard management protocols (Moskowitz et al. 2018). Currently well-designed trials (VICTAS, ACTS, etc.) are ongoing results of which might help us in modifying the practices (Hager et al. 2019; Ascorbic Acid, Corticosteroids, and Thiamine in Sepsis (ACTS) Trial 2019).
   b. *Immune check point inhibitors*: Although we most commonly implicate immune-activation and massive release of cytokines as the major "immune dysregulation" in sepsis, immunosuppression is now being increasingly recognized as a major cause of rising morbidity and mortality in sepsis. Most of

the treatment protocols are designed to tackle the hyperinflammatory state in sepsis not addressing the phase of immunosuppression that follows. It not only reduces the body's ability to clear the primary infection but it also makes them susceptible to secondary infections (Hotchkiss et al. 2009; Boomer et al. 2014). Studies have shown that there is an upregulation of inhibitory molecules like PD-1, PD-L1, CTLA-4, TIM-3, etc. which impairs the innate immune response as well as the adaptive T-cell response. Few studies have also implicated the direct role of these molecules in causing organ injury. Therefore, therapies targeting these targets could potentially change the face of sepsis management (Rudick et al. 2017; Hotchkiss et al. 2013).

c. *Other potential therapies*: GM-CSF, IFN-y, IL-7, IL-15, IVIg, selective Beta-1 blockade, hemoperfusion with polymyxin B, extracorporeal cytokine absorption (CytoSorb®), phage therapy, etc. are other potential therapies that hold promise. However, there is little evidence regarding their efficacy and safety at present and routine use cannot be recommended (Bonavia et al. 2018; Górski et al. 2017; Dellinger et al. 2018; Bo et al. 2011; Döcke et al. 1997; Busani et al. 2016).

After initiation of treatment, patients should be closely monitored for the changes in their clinical, hemodynamic, and laboratory parameters. Timely escalation or de-escalation should be done based on the response to treatment. The goals in the management of sepsis are summarized in Box 2.3.

Box 2.3 Goals in the Management of Sepsis

Goals in the management of sepsis:
- MAP ≥ 65mm Hg
- Lactate < 2mmol/L
- P/F ratio >200
- SpO2 88–92%
- Urine output > .5ml/kg/h
- Hemoglobin > 7g/dl
- Blood glucose < 180mg/dl
- No dyselectrolytemia
- No acid base disbalance

Other measures:
- Place a central venous catheter
- Peptic ulcer prophylaxis
- Venous thrombosis prophylaxis
- Nutritional support
- Pain management
  Sedation vacation

2.10 Readmission

A significant number of patients (around 1/5th of all discharges) are readmitted for recurrent sepsis within 90 days of discharge. 68.6% are admitted with infection at same site and 19% cases have the same organism (53% same site and organism) (DeMerle et al. 2017).

2.11 Sepsis Sequelae

Post-sepsis syndrome is now a well-known entity but greatly under recognized. The odds of developing moderate-to-severe cognitive impairment and functional limitations are higher as compared to the non-sepsis hospitalized patients. In a study that evaluated around 800 critically ill patients, a significant number of patients had a decline in cognitive functioning and had global cognition scores that were similar to those patients with mild Alzheimer's disease and traumatic brain injury (Pandharipande et al. 2013).

A survey from 41 countries with 1731 respondents (79.9% female respondents, age 47.6 ± 14.4 years) with a majority of respondents (47.8%) having sepsis within the last year reported an increase in sensory, integumentary, digestive, breathing, chest pain, kidney and musculoskeletal problems after sepsis. Physical functions such as daily chores, running errands, spelling, reading and reduced libido posed increased difficulty. The survivors also reported varying degrees of anxiety, depression, fatigue and sleep disturbance (Huang et al. 2019). The ABCDEF bundle aims to improve the recovery and outcomes in critically ill patient and should be adhered to. [*A*ssess, Prevent, and Manage Pain, *B*oth Spontaneous Awakening Trials (SAT) and Spontaneous Breathing Trials (SBT), *C*hoice of analgesia and sedation, *D*elirium: Assess, Prevent, and Manage, *E*arly mobility and Exercise, and *F*amily engagement and empowerment] (Barnes-Daly et al. 2018; Marra et al. 2017).

Treating sepsis does not end with the clearance of infection and reversal of organ dysfunction. It is a serious quality of life and cost burden issue that needs to be addressed. Further research in the area of cognitive neurology, establishment of guidelines that address specifically the issue of post-sepsis cognitive impairment is the need of the hour. A social support system should be a part of the institutional care programme for sepsis survivors.

We need to understand that guidelines are applicable to most but not all cases. Basic understanding of pathophysiology and logical decision- making, backed by experience play instrumental role in management of sepsis. Sepsis is still one of the most expensive and the most challenging diseases to treat and win over. Rising incidence of drug resistant organisms has made this battle even more difficult. Therefore, there is an urgent need to invest our resources in order to understand this syndrome better and hope that one day we will be triumphant.

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Tropical Infections in ICU

3

Vettakkara Kandy Muhammed Niyas and Manish Soneja

Infections that are unique to or predominantly seen in the tropical region are referred to as tropical infections. It is a broad term that encompasses a multitude of viral, bacterial, fungal and parasitic infections (Bhargava et al. 2018). These diseases are of significant public health concern as they affect a large section of the world population many of whom do not have access to adequate medical care. With increase in international travel these infections are no longer concern of the developing or underdeveloped nations alone (Marks et al. 2016).

If not identified and treated early, many of these infections can develop life threatening complications that require intensive care. This includes acute respiratory distress syndrome, myocarditis, hepatic failure, acute kidney injury, alteration in sensorium, shock and life threatening metabolic abnormalities (Table 3.1). Patients with these complications are better managed in intensive care units with adequate monitoring and life support systems.

The epidemiology of tropical infections requiring intensive care varies with seasons and regions. Many of these diseases are transmitted by mosquitoes and there is an increase in the incidence of these disease post rainfall due to the increase in vector density (Singhi et al. 2017). Common infections that necessitate hospital care and intensive care are dengue, scrub typhus, acute encephalitis syndromes, malaria and leptospirosis (Chrispal et al. 2010; Mittal et al. 2015). This profile however can vary from region to region and a good knowledge of the local epidemiology of tropical infections is a must for any physician working in these areas. Tropical infections are important cause of morbidity in returning western travellers after visiting these regions. Malaria, enteric fever, dengue fever and leishmaniasis are important tropical infections seen in returning travellers, many of which can have life threatening complications (Marks et al. 2016; Jensenius et al. 2013).

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Table 3.1 Complications of common tropical infections requiring critical care

Tropical infection	Life threatening complications requiring intensive care
Viral infections	
Dengue fever	Shock Fluid accumulation with respiratory distress Severe bleeding Impaired consciousness Liver failure Myocarditis
Yellow fever disease	Hepatic failure Renal dysfunction Severe bleeding
Japanese encephalitis	Impaired consciousness Seizures
Kyasanur forest disease	Severe bleeding Impaired sensorium
Chandipura virus	Impaired sensorium
Nipah virus disease	Impaired consciousness Seizures ARDS
Crimean-Congo haemorrhagic fever	Severe bleeding
Ebola virus disease	Hypovolemic shock Severe bleeding Impaired sensorium Respiratory distress
Rickettsial infections	
Scrub typhus	Impaired consciousness ARDS Myocarditis Renal dysfunction DIC
Murine typhus	Impaired sensorium Renal dysfunction ARDS
Bacterial infections	
Leptospirosis	Renal impairment Hepatic failure Pulmonary haemorrhage ARDS Myocarditis
Enteric fever	Intestinal perforation Impaired sensorium
Traveller's diarrhoea	Hypovolemia
Cholera	Severe diarrhoea and hypovolemia
Melioidosis	Pneumonia Septic shock

Table 3.1 (continued)

Tropical infection	Life threatening complications requiring intensive care
Tetanus	Severe muscle spasms Respiratory muscle spasm (leading to asphyxia) Laryngeal muscle spasm (airway obstruction) Autonomic dysfunction
Diphtheria	Airway obstruction Myocarditis Polyneuropathy (may cause respiratory muscle involvement and autonomic dysfunction)
Parasitic infections	
Malaria	Impaired consciousness Seizures Severe anaemia Hypoglycemia Renal impairment Respiratory distress Severe bleeding Shock
African trypanosomiasis	Impaired sensorium Seizures
American trypanosomiasis	Myocarditis Cardiomyopathy
Visceral leishmaniasis	Severe anaemia Bleeding manifestations Secondary bacterial infections
Amoebiasis	Fulminant colitis and perforation peritonitis Toxic megacolon Liver abscess with rupture (causes peritonitis or pleuro-pulmonary involvement)
Schistosomiasis	Esophageal varices (as a result of portal hypertension) Granulomatous inflammation in bladder causing obstructive uropathy and renal failure Neuroschistosomiasis (spinal cord or cerebral lesions)
Echinococcosis	Cyst rupture Secondary bacterial infections Cysto-bronchial fistula (may cause bronchial obstruction)

3.1 A Syndromic Approach to Diagnosis of Tropical Fevers

Many tropical infections have overlapping clinical features. Reaching a specific diagnosis may be difficult especially in resource limited settings without adequate diagnostic facilities. Moreover many of the serological tests used to diagnose tropical infections may be negative in the early part of the illnesses. A syndromic approach is therefore suggested for the diagnosis and management of undifferentiated tropical infections (Singhi et al. 2014; Karnad et al. 2018a; Kothari et al. 2006).

3.1.1 Fever with Hepatic and/or Renal Impairment

Many tropical infections can be complicated by acute kidney injury, hepatic involvement or both. Mild to moderate elevations in the levels of alanine transaminase (ALT) and aspartate transaminase (AST) levels are common in dengue fever, whereas bilirubin and alkaline phosphatase levels are usually normal (Trung et al. 2010). Elevated serum transaminase levels (ALT and AST >500 IU/ml) are independent predictors of mortality in dengue fever (Jain et al. 2017). Dengue patients with ALT or AST levels ≥1000 IU/L should be classified and managed as severe dengue (World Health Organization 2009).

Hepatic involvement in leptospirosis is characterised by marked increase serum bilirubin leading to jaundice (Fig. 3.1). AST, ALT and alkaline phosphatase are moderately elevated (Katz et al. 2001; Talwani et al. 2011). The kidneys are also

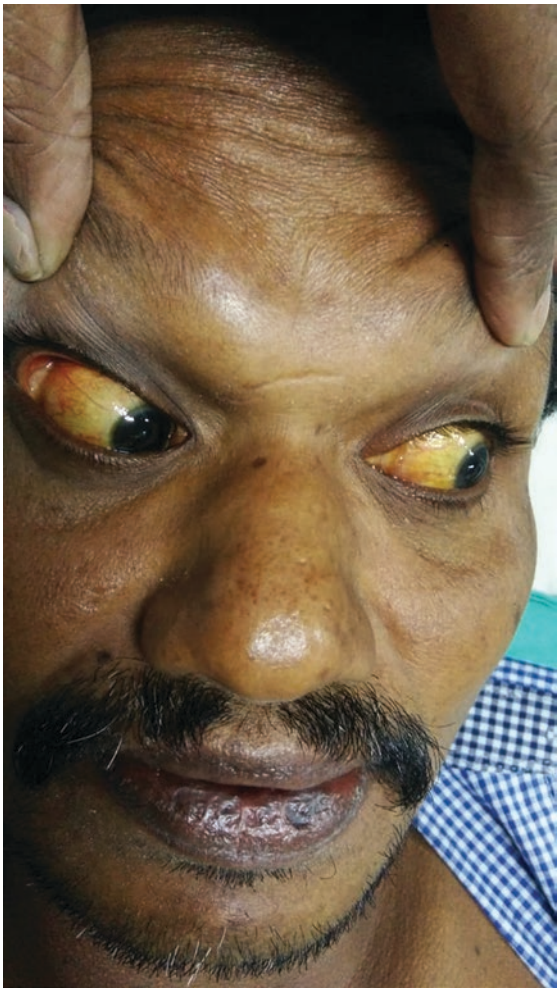

Fig. 3.1 Jaundice and conjunctival suffusion in a patient with leptospirosis (Image courtesy: Latha Rajeevan, Physician, District Hospital, Kannur, Kerala, India)

commonly involved in leptospirosis. Urine analysis may show microscopic haematuria, leucocytes and proteinuria. In severe cases renal involvement can be marked with elevated blood urea nitrogen and serum creatinine (Katz et al. 2001; Levett 2001).

Liver dysfunction in scrub typhus commonly manifests as mild to moderate elevation in serum transaminase levels. Elevated levels of bilirubin and alkaline phosphatase levels are relatively uncommon. Acute kidney injury also complicates a significant number of scrub typhus cases especially in the setting of multi-organ dysfunction (Rajapakse et al. 2017). Though elevated levels of hepatic transaminases are seen commonly in enteric fever, clinically significant hepatitis is uncommon (Sur et al. 2018).

Both hepatic and renal involvement are common in complicated malaria. Hepatic dysfunction in malaria is multifactorial including haemolysis, hepatitis and cholestasis. Acute kidney injury in malaria is due to acute tubular necrosis and is usually oliguric (White et al. 2014).

Liver involvement is characteristic of yellow fever and should be suspected in inhabitants of the endemic areas (South America and sub-Saharan Africa) as well as travellers visiting or returning from these areas (Barnett 2007). In its initial phase it resembles any other viral fever with fever, headache, malaise, myalgia, nausea and vomiting. Most patients enter a period of remission after the initial febrile period. Fifteen to twenty percent of patients may enter a period of intoxication after a brief afebrile period. Fever reappears and patient can develop multiple organ dysfunctions. Liver enzymes are elevated and unlike in other viral fevers AST is elevated more than ALT (Monath 2001). Serum transaminase levels correlate with the severity of the disease (Tuboi et al. 2007). There can be moderate increase in bilirubin levels (5–10 mg/dl), while alkaline phosphatase levels are usually normal. Patients can also develop acute kidney injury, proteinuria and bleeding manifestations.

3.1.2 Fever with Thrombocytopenia and/or Coagulopathy

Thrombocytopenia is seen in almost all patients with symptomatic dengue fever, while coagulopathy occurs in severe cases. Disseminated intravascular coagulation (DIC) can complicate dengue and is a predictor of mortality (Jain et al. 2017). Other viral illnesses that can present with haemorrhagic manifestations include yellow fever, Crimean-Congo haemorrhagic fever, Ebola virus disease and Marburg virus disease. A knowledge of the local epidemiology and patient's detailed travel history may give valuable clues to the diagnosis (Hidalgo et al. 2017).

Ebola and Marburg viruses are two members of the Filoviridae family which can cause life threatening complications. Ebola viral disease has been reported from Central Africa, West Africa and Sudan. An outbreak is currently ongoing in the North Kivu region of the Democratic Republic of Congo. Many patients can develop bleeding manifestations (petechiae, ecchymoses, mucosal bleeding and blood in stools). Severe bleeding may occur towards the terminal phase of the illness. Volume

depletion due to severe vomiting and profuse watery diarrhoea is a major cause of severity and mortality (Schieffelin et al. 2014; Bah et al. 2015). Delirium and seizures can also occur (Chertow et al. 2014).

After its first outbreak in Germany (from imported vervet monkeys from Uganda) all cases of Marburg virus diseases were reported from Africa. It presents as a febrile illness progressing to severe hypotension, shock and coma. Bleeding manifestations occur in many patients, but clinically significant bleeding occurs mostly in terminal stages (Centers for Disease Control and Prevention (CDC) 2005; Kortepeter et al. 2011).

Thrombocytopenia in leptospirosis is transient and usually does not result in DIC (Levett 2001). Thrombocytopenia can occur in scrub typhus as well, and severe cases may be complicated by DIC (Lee et al. 2017). Thrombocytopenia and coagulopathy often complicate malaria, though spontaneous bleeding is uncommon (Karnad et al. 2018b). Thrombocytopenia occurs more commonly in adult patients of enteric fever than in paediatric patients (Azmatullah et al. 2015).

3.1.3 Fever with Rash

A maculopapular/morbilliform rash is common in dengue fever. Petechiae, ecchymosis and mucosal bleeding may indicate a severe disease (Thomas et al. 2007). Similar lesions can occur in other haemorrhagic fevers as well. A transient macular rash may be seen in some patients with leptospirosis (Levett 2001).

A macular or maculopapular rash is common in most of the rickettsial infections. A characteristic eschar can occur at the site of chigger bite in scrub typhus. Its frequency in scrub typhus varies, ranging from 7 to 80% in various studies (Rajapakse et al. 2017). It begins as a papule which enlarges and later necrosis to be covered with a black crust.

Meningococcal infection is to be considered as a differential diagnosis in any patient presenting with fever and rash, though the disease is not limited to the tropics. Skin lesions can be seen in meningococcal meningitis and meningococcemia and can be petechial, purpuric or echymotic lesions (Fig. 3.2).

3.1.4 Fever with Encephalopathy

Fever with altered sensorium in a patient living in a tropical country should raise suspicion of various diagnostic possibilities apart from common bacterial and viral pathogens causing central nervous system infections. Japanese encephalitis (JE) has been considered as the common cause of viral encephalitis in Asian countries. However various other viruses can also give rise to clinically indistinguishable encephalitic syndromes. Dengue virus, Chikungunya virus, Kyasanur forest disease, Chandipura virus and scrub typhus are other important causes of acute encephalitis syndrome (Joshi et al. 2012; Ravi et al. 2019). Cerebral malaria should be another important differential diagnosis in any patient with fever and altered sensorium or seizures.

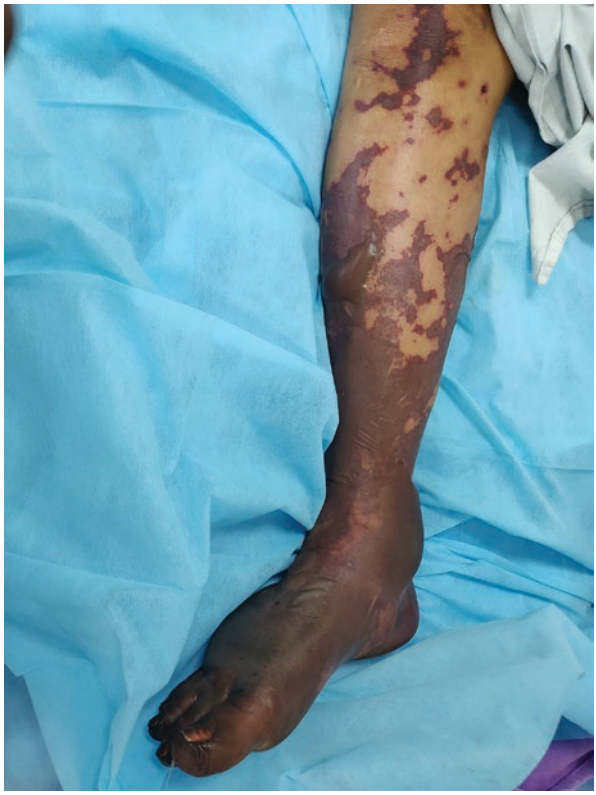

Fig. 3.2 Rash in a patient with meningococcal meningitis

Japanese encephalitis is a mosquito borne flavivirus which is endemic to Asia and western Pacific (Le Flohic et al. 2013; Mackenzie et al. 2006). In endemic areas it predominantly affects the paediatric population (Kabilan et al. 2004). However in non-immune travellers, persons of any age group can be affected. Most of the infections are asymptomatic or mild. However, those who develop neuroinvasive disease can develop life threatening complications. In such patients JE presents as a febrile illness followed after few days with alteration of mental status, focal neurological deficits, seizures and movement disorders. CSF opening pressure may be elevated and CSF studies may show mild to moderate lymphocytic pleocytosis. CSF protein may be mildly elevated and CSF glucose is usually normal. Lesions in the thalamus are characteristic finding on magnetic resonance imaging (MRI) but may not be seen in all patients (Dung et al. 2009). Basal ganglia as well as the brainstem can also be involved. In those who present as an encephalitis syndrome mortality is high (upto 25%) and many of the survivors will have long-term neurological sequelae (Kumar et al. 2017; McNaughton et al. 2018).

Kyasanur forest disease is endemic to the Western Ghats region of southern India (Munivenkatappa et al. 2018). It is a tick borne flavivirus disease which causes a self-limiting febrile disease in most patients. But around 20% of the patients can develop bleeding manifestations or neurological manifestations. Neurological manifestations occur later in the phase of disease in the form of alteration in sensorium,

convulsion and loss of consciousness (Wadia 1975). The Chandipura virus is an arbovirus belonging to the *Rhabdoviridae* family. Outbreaks were reported from Indian states of Gujarat, Maharashtra and Andhra Pradesh (Sudeep et al. 2016). The disease manifests as an acute encephalitis syndrome with high case fatality rate (50–75%) (Rao et al. 2004; Chadha et al. 2005).

In outbreak settings Nipah virus also should be considered as an important cause of encephalitis especially if the patients have coexisting acute respiratory distress syndrome (Banerjee et al. 2019). Nipah has caused outbreaks in Malaysia, Singapore, Bangladesh, Philippines, West Bengal (India) and recently in the southern Indian state of Kerala (Arunkumar et al. 2018).

3.1.5 Fever with Respiratory Distress

Respiratory distress in tropical infection can occur due to various reasons like pneumonia, acute respiratory distress syndrome, myocarditis and pleural effusion. ARDS and myocarditis are well-known complications of tropical infections like dengue, malaria, scrub typhus and leptospirosis (Kumar et al. 2018). Pleural effusion caused by plasma leakage and third space fluid accumulation can cause respiratory distress in dengue patients (Suwarto et al. 2016). Pulmonary haemorrhage is dreaded complication of leptospirosis that can be fatal (Trevejo et al. 1998).

3.2 Laboratory Investigations

3.2.1 Routine Laboratory Investigations

Routine haemogram and blood chemistry can give valuable clues to the diagnosis of tropical fevers (Bhargava et al. 2018). While leucocytosis is common in leptospirosis, leucopenia is seen in most cases of viral illnesses including dengue fever. As mentioned above thrombocytopenia occurs in many tropical infections. A rising haematocrit may indicate haemocencentration in dengue fever. Alterations in hepatic and renal parameters occur in many tropical infections and the pattern of involvement may indicate specific diagnosis (Table 3.2). Creatine phosphokinase may be elevated in leptospirosis (Johnson et al. 1975). A peripheral smear is of utmost importance for the diagnosis of malaria.

3.2.2 Culture and Sensitivity Testing

Appropriate microbiological investigations should be sent for all critically ill patients with suspected tropical infections. If any focus of infection is suspected, appropriate samples should be sent for gram staining, bacterial culture and sensitivity testing. Similarly if a fungal infection is suspected, samples should be send for microscopy (KOH staining, Calcofluor-white stain, etc.) and fungal culture and sensitivity testing.

Table 3.2 Clinical and laboratory features of important tropical infections

Tropical infection	Epidemiology	Clinical features	Abnormalities in routine laboratory testing	Diagnosis	Specific management
Dengue fever	Caused by: Dengue virus (serotypes 1–4) Principle vector: Aedes aegypti mosquitoes Incubation period: 4–6 days Seasonal increase in rainfall leads to increase in the vector density and an increase in number of dengue cases. However many tropical countries are hyperendemic for dengue and cases can present in any season	Fever (usually lasting for 2–7 days) Headache Myalgia Retroorbital pain Rash and haemorrhagic manifestations	Leucopenia Thrombocytopenia Elevated haematocrit Elevation in transaminase levels	Dengue NS1 antigen detection (first 6 days of illness) Nucleic acid detection by RT-PCR (first 5 days of illness) IgM ELISA (after 5 days of illness)	Fluid resuscitation for shock Blood transfusion in patients with significant internal bleeding Platelet transfusion in those with platelet count less than 10,000/mm^3 and/ active bleeding
Leptospirosis	Caused by Leptospira spp. Incubation period: 1–2 weeks Transmitted commonly by exposure to water contaminated by rat urine. Increase in number of cases can be seen following rainfall and flooding in endemic areas	Fever (1–2 weeks duration) Muscle pain Calf muscle tenderness Conjunctival suffusion Jaundice Oliguria	Leucocytosis Thrombocytopenia Hyperbilirubinemia (marked increase may be seen) Moderate increase in hepatic transaminase levels Elevated blood urea, serum creatinine, creatinine phosphokinase Urine analysis may show proteinuria, WBCs and RBCs	IgM ELISA is the most commonly available test. May be negative in early phase of illness Microscopic agglutination test (MAT) and PCR are more sensitive and specific, but are not widely available and are expensive	For critically ill patients intravenous therapy is preferred. Effective drugs include crystalline penicillin (1.5 MU IV q6h) for 7 days Alternate agents Ceftriaxone (2 g IV q24h) or Doxycycline (100 mg IV q12h)

(continued)

Table 3.2 (continued)

Tropical infection	Epidemiology	Clinical features	Abnormalities in routine laboratory testing	Diagnosis	Specific management
Scrub typhus	Scrub typhus is caused by *Orientia tsutsugamushi* and is transmitted by the bite of the infected larval stages (chiggers) of the trombiculid mites during feeding Incubation period: 7–10 days It is endemic in many countries in the Asia-Pacific region including China, India, Japan, Korea, Thailand, Indonesia and Sri Lanka	Fever (usually prolonged; median duration of 2 weeks) Headache Myalgia A characteristic eschar at the site of chigger bite may be seen	Leucopenia or leucocytosis Thrombocytopenia Mild to moderate increase in transaminase levels Creatinine may be elevated	IgM ELISA is the test is widely available Indirect fluorescent antibody test is considered as gold standard in serology Weil–Felix test has poor sensitivity and specificity Serological tests may be negative in early part of the illness	Doxycycline 100 mg IV/PO q12h × 7 days OR Azithromycin 500 mg PO/IV q24h × 3 days
Enteric fever	*Caused by Salmonella enterica* serotype Typhi Incubation period: 10–14 days Transmitted usually through contaminated food and water It is more prevalent in areas with poor sanitation	Fever (usually prolonged) Diarrhoea or constipation Headache	Leucopenia or leucocytosis Mild to moderate increase in serum transaminase levels	Blood culture (sensitivity: 50–70%) Bone marrow culture is more sensitive Serological tests including the Widal test are unreliable	Ceftriaxone 2 g IV q12h for 10 to 14 days OR Azithromycin 1 g PO/IV for 5–7 days

Malaria	Transmitted by the bite of female anopheles mosquito Incubation period: 1–4 weeks Malaria is endemic to most of the tropical countries. Severe disease is usually caused by *P. falciparum* but can occur in infections due to other species also	High grade fever with chills and sweating Malaise Headache Abdominal pain Splenomegaly	Anaemia Thrombocytopenia Coagulation abnormalities Increased bilirubin, hepatic transaminases Elevated serum creatinine Metabolic acidosis	Direct microscopy of giemsa stained peripheral blood smears (cannot detect low level parasitaemia) Rapid diagnostic tests: based on detection of malarial antigens Commonly used antigens include HRP2, LDH and aldolase. These tests are fairly accurate and easy to use	Parenteral artesunate is the drug of choice for severe malaria. It should be given atleast for 24 h and till oral administration is possible (Dose: 2.4 mg/kg/dose stat followed by at 12 h, 24 h and then daily once) Treatment should be completed with a three course of artemisinin combination therapy
Yellow fever	Caused by yellow fever virus, a flavivirus and transmitted by the bite of Aedes aegypti mosquitoes Endemic to sub-Saharan Africa and South America	Disease begins as a non-specific viral illness with fever, headache, malaise and myalgia. This may be followed by an afebrile period. Around 15% patients enters a period of intoxication characterised by hepatic and renal dysfunction	Leukopenia Elevated liver enzymes, (AST >> ALT) Moderately elevated levels of Bilirubin Azotemia, elevated creatinine, and significant proteinuria	Anti YF IgM antibody detection ELISA Cross reactivity with other Flavivirus can occur) IgM antibodies can persist after vaccination RT-PCR High sensitivity and specificity Can differentiate between wild virus and 17D vaccine strain LAMP (loop-mediated isothermal amplification) RT-PCR: rapid, sensitive test Do not require thermocycler, can be used in field settings	No anti-viral treatment available Supportive care, including fluid management, correction of metabolic abnormalities, correction of coagulopathy, dialysis, treatment of secondary bacterial infections

Many tropical infections can be complicated by secondary bacterial infections leading to bacteraemia and sepsis (Syue et al. 2018; West et al. 2014). Blood culture is therefore a mandatory investigation in these patients. Blood culture is the diagnostic investigation for enteric fever and is positive in about 50–70% of patients. Bone marrow culture offers sensitivity more than 90% in enteric fever and may be attempted if diagnosis remains elusive despite routine tests (Mogasale et al. 2016). Blood and urine culture for the diagnosis of leptospirosis are of low sensitivity and are seldom clinically useful.

3.2.3 Serological Tests

Specific serological tests for tropical infections should be done based on pre-test probabilities (Table 3.2). Considering the potential life threatening complications rapid diagnostic tests are often helpful in guiding therapy.

Serological tests for the diagnosis of dengue fever should be chosen based on the day of illness. In the initial 5 days of illness NS1 antigen detection by ELISA is preferred, while after 5 days IgM antibody by ELISA is used for diagnosis. Rapid tests for the diagnosis of dengue though less time consuming are not completely reliable (Hunsperger et al. 2009, 2014).

Peripheral blood smear examination has been traditionally used as the standard test for the diagnosis of malaria. However the procedure is operator dependent and cases with low level of parasitaemia can be missed (Kilian et al. 2000). Rapid diagnostic tests based on malarial antigens have revolutionised the diagnosis of malaria. The RDT kits are easy to use and give results in a short span of time. Commonly used kits are immunochromatography based flow through assays which detects one or more malarial antigens (histidine-rich protein 2 (HRP2), *Plasmodium* lactate dehydrogenase (pLDH) and aldolase). Current kits can also differentiate between Plasmodium falciparum malaria from malaria due to other species. The sensitivity and specificity of these RDTs are over 90% (Wilson 2012).

The microscopic agglutination test (MAT) considered as the reference standard serological test for the diagnosis of leptospirosis is cumbersome to perform and is not readily available. It also requires paired sera demonstrating a fourfold rise in titre for a definitive diagnosis. Various RDTs are commercially available which may help in presumptive diagnosis especially in acute settings. For confirmation it is recommended to perform testing by two different RDTs (National Centre for Disease Control 2015). IgM Immunofluorescence assay (IFA) is considered as the gold standard serological test for the diagnosis of scrub typhus. IgM ELISA is an alternative test with comparable sensitivity and specificity. IgM rapid flow assay is a point of care test that may be useful in resource limited setting (Gupta et al. 2016). Currently available serological tests for the diagnosis of enteric fever are not completely reliable (Wijedoru et al. 2017).

It should be emphasised that many serological tests may be negative in the initial phase of illness, and a negative serological test should not deter the clinician from initiating specific antimicrobial therapy in critically ill patients, especially if clinical possibility is high.

3.3 Management of Critically Ill Patients with Tropical Infections

The initial focus of management should be on correction of haemodynamic instability, hypoxemia, protection of airway and early initiation of antimicrobial agents. Hypovolemia and hypoperfusion can complicate many tropical infections. Moreover many tropical infections may be complicated by super added sepsis. Fluid and vasopressor therapy should be administered in accordance with the current sepsis guidelines (Singer et al. 2016; Rhodes et al. 2017). Fluid resuscitation is of at most importance in the management of dengue fever (Dutta et al. 2011). Hypoxemia and ARDS may require invasive or non-invasive ventilation. Endotracheal intubation may be required for the protection of airway in those patients with depressed sensorium.

3.3.1 Empirical Antimicrobial Therapy

If a tropical infection is suspected in a critically ill patient, appropriate antibiotics should be initiated without waiting for confirmatory laboratory residents. An attempt to make a clinical diagnosis based on the local epidemiology, travel and exposure history, physical examination and basic laboratory investigations should be made. A syndromic approach as mentioned above can be helpful in the initiation of antibiotics. Often a specific diagnosis may take time and meanwhile a combination of antibiotics may have to be used. For example, a combination of intravenous artesunate, ceftriaxone and doxycycline can cover most of the tropical infections and may have to be used in critically ill patients with suspected tropical infections awaiting a specific diagnosis (Karnad et al. 2018a).

3.4 Management Issues in Specific Tropical Infections

3.4.1 Dengue Fever

Most complications in dengue fever occur during the critical phase of illness (day 3–7 of illness). During this period there is an increase in capillary permeability leading to plasma leakage. When patients lose a critical amount of plasma, shock develops. Thrombocytopenia and coagulation abnormalities during this time lead to bleeding manifestations which sometimes can be severe.

Patients with severe dengue should be managed ideally in an intensive care setup. Criteria for severe dengue is given in Table 3.3.

Fluid management with intravascular volume repletion forms the cornerstone of management of patients with plasma leakage. Crystalloids can be used as the fluid for initial resuscitation as randomised studies has shown no significant advantage of colloids over crystalloids (Wills et al. 2005). Details of fluid management in dengue patients with shock is summarised in Figs. 3.3 and 3.4 (World Health Organization 2009). In patients with significant bleeding leading to hypovolemia blood transfusion should be

Table 3.3 Criteria for severe dengue (World Health Organisation 2009)

Severe plasma leakage – Dengue shock syndrome – Fluid accumulation with respiratory distress
Severe bleeding as evaluated by the clinician
Severe organ involvement – Liver: AST or ALT ≥ 1000 IU/L – CNS: impaired consciousness – Heart and other organs

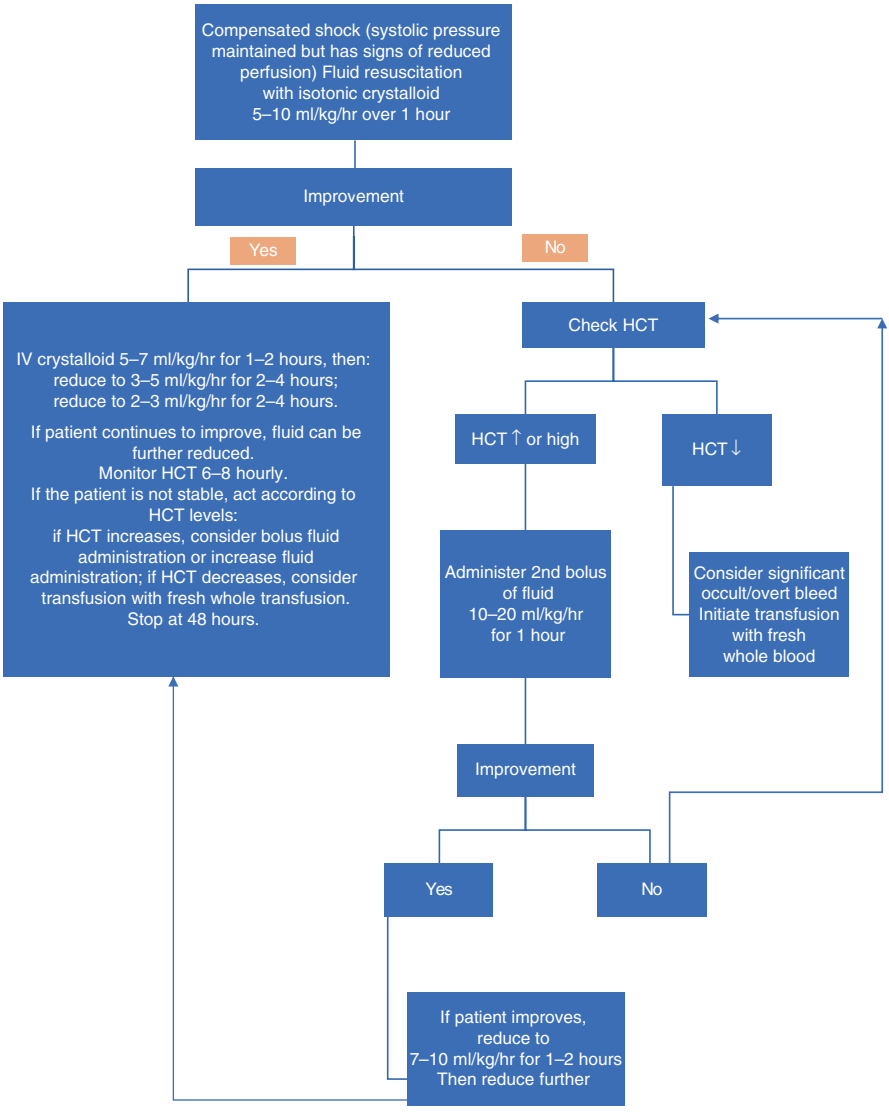

Fig. 3.3 Fluid management in Dengue fever with compensated shock (World Health Organisation 2009)

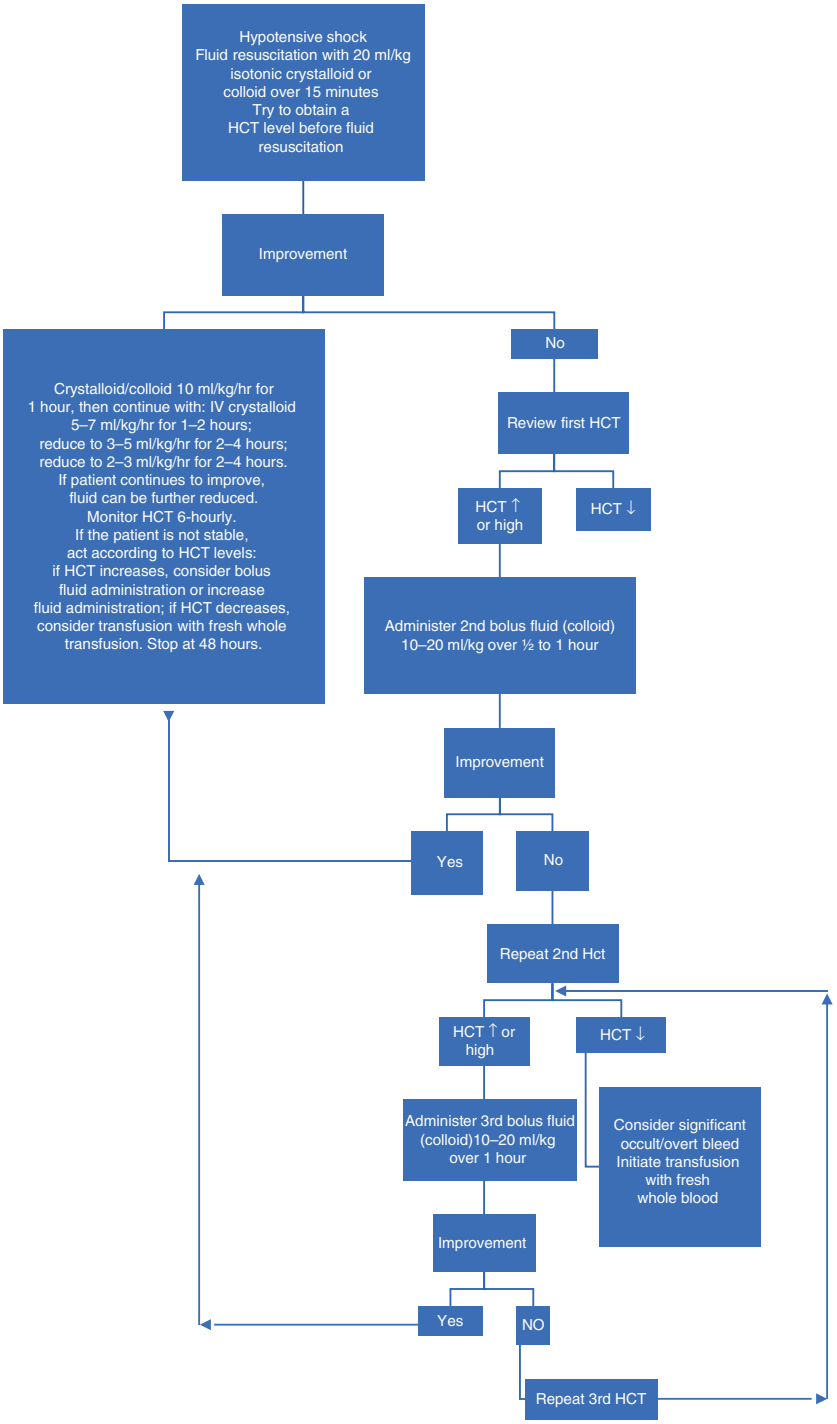

Fig. 3.4 Fluid management in Dengue fever with hypotensive shock (World Health Organization 2009)

Table 3.4 Criteria for severe malaria (from (WHO 2015))

Severe falciparum malaria is defined as one or more of the following in the absence of an identified alternative cause and in the presence of *P. falciparum* parasitaemia
Impaired consciousness—Glasgow coma score <11 in adults or Blantyre coma score <3 in children
Prostration—generalised weakness so that a person is unable to sit, stand or walk without assistance
Multiple convulsions—more than two episodes within 24 h
Acidosis—a base deficit of >8 mEq/L, a plasma bicarbonate level of <15 mmol/L, or venous plasma lactate ≥5 mmol/L. Clinical indicators of acidosis include rapid, deep, laboured breathing
Hypoglycemia—blood or plasma glucose <40 mg/dL (<2.2 mmol/L)
Severe malarial anaemia—haemoglobin concentration ≤5 g/dL or haematocrit ≤15% in children <12 years of age (<7 g/dL and <20%, respectively, in adults) with parasite count >10,000/mcL
Renal impairment—plasma or serum creatinine >3 mg/dL (265 mcmol/L) or blood urea >20 mmol/L
Jaundice—plasma or serum bilirubin >50 mcmol/L (3 mg/dL) with a parasite count >100,000/mcL (approximately 2%)
Pulmonary edema—radiographically confirmed or oxygen saturation <92% on room air with respiratory rate >30/min, often with chest indrawing and crepitation on auscultation
Significant bleeding—including recurrent or prolonged bleeding from the nose, gums, or venipuncture sites, hematemesis, or melena
Shock—compensated shock is defined as capillary refill ≥3 s or temperature gradient on leg (mid to proximal limb) but no hypotension. Decompensated shock is defined as systolic blood pressure <70 mmHg in children or <80 mmHg in adults, with evidence of impaired perfusion (cool peripheries or prolonged capillary refill)
P. falciparum parasitaemia >10% (>500,000/mcL)
Severe *P. vivax* malaria is defined as falciparum malaria, except that there are no parasite density thresholds

given. There is no role for prophylactic platelet therapy in the absence of severe thrombocytopenia (<10,000/mm^3) or active bleeding manifestations (World Health Organization 2009; Dutta et al. 2011). There is no sufficient evidence to support the use of corticosteroids in the management of dengue fever (Zhang and Kramer 2014).

3.4.2 Malaria

Severe malaria is a life threatening emergency and needs intensive monitoring and critical care. The definition of severe *P. falciparum* and *P. vivax* malaria is given in Table 3.4. All patients with severe malaria, irrespective of the infecting species, should be treated with parenteral artesunate for atleast 24 h and until oral therapy is tolerated, after which treatment should be completed with artemisinin based combination therapy (artemether plus lumefantrine, artesunate plus amodiaquine or dihydroartemisinin plus piperaquine) for three days (WHO 2015; Sinclair et al. 2012). The same treatment is recommended in pregnant and lactating women as well. If artesunate is not available intramuscular, artemether is preferred over quinine in treating severe malaria (Esu et al. 2014).

Apart from anti-malarial therapy supportive care and management of complications is of utmost significance in the management of severe malaria. Fluid status should be carefully assessed and managed accordingly. Impaired consciousness is a common complication of severe malaria. Airway has to be protected in such patients and in severe cases intubation may be needed to secure the airway. Convulsions should be managed with short acting benzodiazepines (diazepam, lorazepam or midazolam). Patients should be monitored for hypoglycaemia, and those with blood glucose level less than 40 mg/dl should be treated with continuous dextrose infusion. Severe anaemia (Haemoglobin <7 g/dL in adults) requires treatment with blood transfusion. Severe acute kidney injury and metabolic acidosis may warrant use of renal replacement therapy. Patients with poor sensorium may require endotracheal intubation for airway protection. ARDS in these patients should be managed as per standard ARDS protocols with lung protective ventilation (Taylor et al. 2012).

3.4.3 Leptospirosis

Antibiotics should be started at the earliest in critically ill patients of leptospirosis (Tubiana et al. 2013). Parenteral therapy is indicated in these patients. Effective agents include crystalline penicillin, doxycycline, ceftriaxone and cefotaxime. Antibiotics are usually continued for 7 days.

Acute kidney injury is common in severe leptospirosis. Pre-renal AKI may respond to fluid replacement; however, many patients will require renal replacement therapy. Hypokalemia is common, serum potassium levels should be monitored regularly and levels should be corrected if indicated.

The role of steroids in the management of severe leptospirosis is controversial. It has been tried in cases of severe leptospirosis with pulmonary involvement. While the only randomised control trial in this regard found that corticosteroids were ineffective and increased the risk of nosocomial infections, four prospective studies found benefit in those treated with steroids (Rodrigo et al. 2014; Azevedo et al. 2011).

3.4.4 Scrub Typhus

The preferred antibiotic is doxycycline given for a duration of seven days. Other effective agents include azithromycin, rifampicin and chloramphenicol (Jang et al. 2014).

Scrub typhus can be complicated by ARDS, meningo-encephalitis, myocarditis and disseminated intravascular coagulation and should be managed as accordingly as they arise.

3.4.5 Acute Encephalitis Syndromes

All patients presenting with acute encephalitis syndrome should be first stabilised and airways should be protected. Convulsions should be initially managed using short acting benzodiazepines. In case of recurrent seizures or status epilepticus, other anti-convulsants may have to be used. All metabolic abnormalities should be

corrected. A lumbar puncture and CSF analysis should be done for all patients presenting with acute onset fever and altered sensorium. If the CSF is showing possibility of pyogenic meningitis, patients should be started on ceftriaxone and vancomycin pending culture reports. In case an encephalitis syndrome is suspected an MRI of the brain can be done. If MRI is suggestive of Herpes encephalitis (temporal lobe involvement), IV acyclovir should be initiated. If thalamic involvement is prominent, Japanese encephalitis can be suspected. If the patient has other systemic involvement in addition to fever and altered sensorium, patients should be worked up for malaria, dengue, scrub typhus and leptospirosis. Empirical doxycycline should be added to treatment if scrub typhus or leptospirosis is suspected. For definitive diagnosis serological investigations and nucleic acid amplification tests (NAAT) in serum and CSF will have to be sent (Misra et al. 2017).

3.5 Conclusion

Tropical infections can cause life threatening complications requiring intensive monitoring and treatment. They account for a significant proportion of ICU admissions in the tropical countries. Early identification of the clinical syndrome and prompt initiation of empirical therapy is of paramount importance. Supportive therapy in the ICU including fluid management, correction of electrolyte imbalances and ventillatory support is also essential for successful management of critically ill patients with tropical infections.

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Severe Community-Acquired Pneumonia

4

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Key Points

- Severe community-acquired pneumonia (SCAP) is a serious form of infection of the lung parenchyma acquired in the community that requires admission to the intensive care unit and has a high risk of mortality.
- Immunocompromised patients and those with medical co-morbidities are more likely to develop SCAP.
- *Streptococcus pneumoniae* remains the most common causative pathogen of SCAP; other common offenders being viruses, *Hemophilus influenzae* and atypical organisms like *Legionella*. Less frequently, gram-negative bacilli and *Staphylococcus aureus* may cause SCAP, particularly in hosts with risk factors for these pathogens.
- Diagnostic evaluation includes a chest radiograph to confirm the diagnosis, and the assessment of the severity of the disease using tools to assess organ dysfunction such as arterial blood gas analysis, renal and liver function tests, blood counts, and coagulation profile.
- Scoring systems such as IDSA/ATS criteria, Pneumonia Severity Index, CURB-65, and SMART-COP may be used to assess the severity, mortality risk, and the requirement of admission to the intensive care unit.
- Blood, respiratory samples (sputum, endotracheal aspirate, or bronchoalveolar lavage) and, if present, pleural fluid must be sent for microbiological analysis as early as possible.
- Empirical antibiotics must be instituted at the earliest after the diagnosis is made. The antibiotic regime must be concordant with local guidelines formulated according to the current scientific evidence, prevalent epidemiology, and local antibiotic susceptibility data.

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- A combination of a β-lactam antibiotic (such as amoxicillin-clavulanate, ceftriaxone, cefotaxime) and a macrolide (azithromycin or clarithromycin) is the usual choice in most patients, unless they have risk for *Pseudomonas*, *Staphylococcus aureus*, or resistant organisms. Antibiotics must be de-escalated once a pathogen has been identified.
- The total duration of antibiotics in most cases is 5–7 days.
- Supportive treatment including assisted ventilation for respiratory failure and ARDS, vasopressors and inotropes for septic shock, chest drain for empyema, and others are instituted, as required. Glucocorticoids use may benefit certain subsets of SCAP as an adjunctive treatment.
- Newer biomarkers to assess severity and predict outcomes are being studied. Personalized management, using the principles of microbiomics, genomics, transcriptomics, metabolomics, and immunology, is the vision for the future.

4.1 Introduction and Definition

Community-acquired pneumonia (CAP) refers to an infection of the lung parenchyma acquired in the community (outside a healthcare setting). CAP forms a part of a larger group of diseases known as lower respiratory tract infections (LRTIs). The term "severe CAP (SCAP)" signifies a more serious form of pneumonia acquired in the community. The consensus guidelines on the diagnosis and management of CAP laid down by the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) have defined SCAP as pneumonia that requires ICU admission (Mandell et al. 2007). In these guidelines, the criteria for admission to the ICU include the requirement of invasive mechanical ventilation or that of vasopressors for septic shock or the presence of at least three markers of organ dysfunction that predict higher mortality (Mandell et al. 2007). In real life, though, the actual reasons for admission to the ICU and the predicted outcomes of CAP may vary across centers depending on the geographical locale, local policies, hospital resources, and prevalent microorganisms. There are various other scores, discussed later in this chapter, which help in categorizing the severity of CAP. However, for the purpose of this chapter, we define SCAP according to the IDSA/ATS criteria, as they are the most widely accepted criteria till date.

4.2 Epidemiology

According to the World Health Organization (WHO) estimates 2016, LRTIs accounted for around three million deaths worldwide (World Health Organization 2018). They ranked fourth globally and first among the low-income nations as the leading causes of death. In India, LRTI resulted in 63.1 deaths per 100,000 population and were the fourth biggest killer after ischemic heart disease, chronic obstructive pulmonary disease (COPD), and stroke (World Health Organization 2018). Even these figures may be an underrepresentation since sepsis, the most common cause of which is pneumonia, is coded separately. Similarly, neurological disorders

like parkinsonism and stroke, where the final cause of death is commonly pneumonia, are coded separately (Wunderink and Waterer 2014). In India, as much as 20% of mortality due to infectious diseases has been attributed to LRTI (Gupta et al. 2012). The reported mortality of CAP varies from 3.3% to 11% in studies from India (Gupta et al. 2012). No data on SCAP in adults are available from India. According to one estimate, in 2010, about 3.6 million (3.3–3.9 million) episodes of severe pneumonia and 0.35 million (0.31–0.40 million) all cause pneumonia deaths occurred in children less than 5 years of age (Farooqui et al. 2015).

Community-acquired pneumonia is the third leading cause of hospital admissions (Rider and Frazee 2018). About 20–40% cases of CAP require hospital admission and 5–10% of these need ICU admission (Walden et al. 2014). The 30-day mortality rates and re-admission rates among hospitalized patients with CAP are 10–12% and 18%, respectively (Musher and Thorner 2014). In a large study of patients with SCAP admitted to the ICU across 17 countries of Europe, the 28-day and 6-month mortality were 17% and 27%, respectively (Walden et al. 2014). Despite advances in medicine and technology, the mortality in CAP has not significantly improved over the last 40 years (Rider and Frazee 2018). The data on trends in the mortality due to CAP are conflicting. In an analysis of 800 SCAP patients (requiring ICU admission) enrolled in the CAP Organization International cohort from 2001 through 2013, mortality was found to have increased from 15.7% in the initial years (2001–2004) to 24.3% towards the end (2008–2013) (Cavallazzi et al. 2015). On the contrary, a retrospective single-center cohort study of 458 patients with SCAP concluded that though the incidence of SCAP and its severity increased through the years from 1999 to 2013, the mortality reduced by 18% (Valles et al. 2016). This was attributed to a reduced incidence of bacteremia and increased use of appropriate antibiotics.

4.3 Pathogenesis and Risk Factors

The pathogenesis of CAP involves establishment of an infection of the lung parenchyma by a virulent micro-organism by overwhelming the host defense (Sligl and Marrie 2013). The severity of CAP may depend on certain host- and pathogen-related factors (Table 4.1). Factors such as advanced age, immunocompromised states, malnutrition, and co-morbidities (such as diabetes mellitus, chronic liver, or kidney disease) are well known and easily identifiable factors that increase the risk of severe pneumonia (Falguera et al. 2005). In fact, significant co-morbidities are present in 46–66% of all SCAP patients (Mandell et al. 2007; Torres et al. 2013). Other less obvious factors that may result in SCAP include the load of the infecting micro-organism, the virulence of the pathogen, and subtle (both known and unknown) genetic factors of the host (Sligl and Marrie 2013; Waterer and Rello 2011; Nimmo 2012; Sole-Violan et al. 2011; Rello and Perez 2016).

Recent studies have evaluated the normal lung immune response to infection. Cytokine levels (both pro-inflammatory and anti-inflammatory) in the plasma and the lungs are far higher in SCAP patients and are associated with both ICU admission and mortality (Kellum et al. 2007; Antunes et al. 2002; Martinez et al. 2011; Ramirez et al. 2011). The reasons for this exaggerated response in some individuals

Table 4.1 Risk factors for developing severe community-acquired pneumonia

Delayed diagnosis and absence of antibiotic therapy before hospitalization
Advanced age
Co-morbid illness (e.g., chronic respiratory illness like COPD, cardiovascular disease, diabetes mellitus, neurologic illness, renal insufficiency, malignancy)
Cigarette smoking
Alcohol abuse
Increased pathogen load or virulence
Pharmacological or pathological immunosuppression
Host genetic polymorphisms affecting the inflammatory and immunological response

are not well known (Kellum et al. 2007). The administration of the first dose of antibiotics may also cause a massive surge in cytokine levels in some patients. Analysis of transcriptomic data of SCAP patients has led to the detection of defects in host immune response and aberrations in inflammatory milieu such as T-cell exhaustion, endotoxin tolerance, HLA-receptor deactivation, and a metabolic switch to the glycolytic pathway (Hopp et al. 2018). Epigenetic influences like chromatin remodeling have also been detected (Hopp et al. 2018). Apart from this, a variety of largely unknown factors affecting the host response to infection are probably involved in the predisposition to SCAP. These concern metabolomics, microbiomics, genomics, and subtle variations in the immune landscape of the host.

4.4 Etiologic Agent

Even with the availability of an extensive microbiological diagnostic armamentarium, a definite etiological agent is identified in only about 50% cases of SCAP (Mandell et al. 2007; Rider and Frazee 2018). This implies not only the limitations of the existing diagnostic tools but also the lack of awareness on several microorganisms that are responsible for CAP and SCAP. The most common organism implicated in SCAP remains pneumococcus (*Streptococcus pneumoniae*), which is also the commonest organism isolated in any severity of CAP (Prina et al. 2015; Said et al. 2013). The other common organisms causing SCAP include *Hemophilus influenzae*, atypical organisms, viruses, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, other gram-negative bacilli (GNB), and anaerobes (Sligl and Marrie 2013). About 6% of cases are caused by the so-called PES (*Pseudomonas aeruginosa*, extended-spectrum β-lactamase producing *Enterobacteriaceae*, and methicillin resistant *Staphylococcus aureus*) pathogens (Cilloniz et al. 2019).

S. pneumoniae is the etiologic agent in about 30% of all cases admitted to the ICU with a known etiology (Walden et al. 2014; Valles et al. 2016). In as many as 40% cases, the isolate may be resistant to penicillin and other antibiotics in vitro studies (Rider and Frazee 2018; Cherazard et al. 2017). Macrolide resistance in pneumococcus has become common with resistance rates ranging from 27% in the USA to as high as 90% in certain parts of Japan (Rider and Frazee 2018). The clinical relevance of the same is uncertain (Mandell et al. 2007; Rider and Frazee 2018).

Infections with atypical organisms such as *Legionella*, *Mycoplasma,* and *Chlamydia* species are also common and often co-exist with simultaneous typical

bacterial infection in SCAP. Together, these pathogens may be responsible for 22% of cases of CAP (Prina et al. 2015; Arnold et al. 2007). Hence, it is recommended that the empiric choice of antibiotic therapy for severe CAP should always include antibiotics that are active against atypical organisms (Mandell et al. 2007). Occasionally, tuberculosis may present as SCAP, and may be associated with ARDS (Agarwal et al. 2005; Muthu et al. 2017, 2018a, b). In an endemic region, a high index of suspicion for tuberculosis may thus be kept. Viruses also form a large group among microbes causing SCAP; the commonly implicated ones being influenza, rhinovirus, respiratory syncytial virus, metapneumovirus, and the coronavirus (Musher and Thorner 2014; Klein et al. 2016). The pandemic influenza A H1N1/09 virus caused a major pandemic of viral pneumonia in 2009 and was associated with SCAP in 20% of hospitalized patients (Lum et al. 2009). The virus continues to circulate in several regions of the world causing SCAP. Besides, influenza A H1N1/09 virus, the H5N1 influenza virus, the severe acute respiratory syndrome (SARS) coronavirus, and the Middle East respiratory syndrome (MERS) coronavirus have been implicated to cause SCAP, in the form of outbreaks. In 2019, a novel coronavirus, called the SARS-CoV-2 was reported from China. The virus has caused a pandemic of a severe respiratory illness called the coronavirus disease-19 (COVID-19) in 2020.

Staphylococcus aureus can lead to a severe bilateral necrotizing pneumonia, often related to toxin production by the organism (Sligl and Marrie 2013). The organism is more likely to be isolated in elderly patients, in patients with an influenza infection, intravenous drug abusers, in those with underlying cardiopulmonary co-morbidities or end-stage renal disease, and in those living in crowded surroundings or those with frequent or recent contact with healthcare set-up (particularly recent use of antibiotics like fluoroquinolones) (Mandell et al. 2007; Klein et al. 2016; Venezia et al. 2001; Teng et al. 2019). *Staphylococcus aureus* causing SCAP may be drug resistant, and is known as community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA). CA-MRSA is distinct from the nosocomial strain of MRSA and is clonal in origin. Although more virulent than hospital-acquired MRSA, CA-MRSA is often sensitive to common non-beta lactam antibiotics (such as clindamycin, trimethoprim-sulfamethoxazole, and tetracycline) (Rubinstein et al. 2008).

Enteric GNB and anaerobes may infrequently be isolated in SCAP. The frequency of gram-negative CAP is difficult to define. In a prospective surveillance study conducted by Asian Network for Surveillance of Resistant Pathogens (ANSORP), 93 of 912 CAP patients (10.1%) had isolation of GNB, with *Klebsiella pneumoniae* being the commonest isolate followed by *Pseudomonas aeruginosa* (Kang et al. 2008). Mortality was higher in the GNB group than non-GNB group. Infection with GNB was more commonly associated with septic shock and was more likely to occur in smokers and those with underlying malignancy or cardiovascular diseases. Patients most likely to have CAP due to GNB are those who have recently been exposed to antibiotics, or were hospitalized, or have multiple medical co-morbidities (including alcoholism) or structural lung diseases.

Around 11% of SCAP patients may have a polymicrobial etiology, especially when they present with ARDS or when they have underlying COPD (Cilloniz et al. 2016a, 2011).

4.5 Diagnostic Evaluation

The evaluation in SCAP is aimed at making a diagnosis of CAP, assessing its severity, identifying complications, deciding the place of care, and identifying the etiologic agent. A focused history and physical examination along with a chest radiograph are usually sufficient to make a diagnosis of CAP. Cough, sputum production, fever, dyspnea, and pleuritic chest pain are the cardinal symptoms of CAP. Patients with SCAP, due to host or pathogen-related factors, have a more profound systemic inflammatory response and are thus more likely to have tachypnea, tachycardia, hypotension, confusion, temperature >40 °C, or hypothermia (Sligl and Marrie 2013). Immunocompromised or elderly individuals may mount an inadequate inflammatory response to CAP and may thus have an atypical presentation (Fernandez-Sabe et al. 2003). In fact, a lack of pleuritic chest pain and an absence of typical symptoms are often associated with poorer prognosis (Musher and Thorner 2014; Fernandez-Sabe et al. 2003; Cilloniz et al. 2016b).

A chest radiograph should be obtained in all suspected cases of SCAP. Illustrative examples of radiographic abnormalities in SCAP are depicted in Fig. 4.1. Consolidation of a part or whole of the lung is the *sine qua non* of CAP (Fig. 4.1a). Air bronchograms are commonly seen inside the area of consolidation. The consolidation can be localized to a subsegment, segment, or lobe of the lung or can sometimes involve the entire lung. The involvement can also be in the form of more extensive fluffy airspace opacities suggesting bronchopneumonia (Fig. 4.1b) or in the form of interstitial or reticular opacities (Fig. 4.1c). Appearance of specks of airspaces within the area of consolidation indicates the development of necrotizing pneumonia (Fig. 4.1d). Multilobar radiographic abnormalities, bilateral infiltrates, and rapidly progressive radiographic abnormalities during therapy suggest severe pneumonia and are associated with poor prognosis (Marti et al. 2012). The differential diagnoses and mimics of SCAP are described in Table 4.2.

Several of the clinical and radiological features have been incorporated into various scoring systems, along with laboratory data, in diverse combinations to define SCAP. Complications such as sepsis, ARDS, multi-organ dysfunction syndrome (MODS), lung abscess, and parapneumonic effusion/empyema should be identified at the time of diagnosis and during the course of the illness. Computed tomography (CT) of the chest may sometimes be required to confirm pneumonia, characterize the pattern for clues to possible etiology, detect complications like lung abscess and empyema, and exclude alternate possibilities.

4.5.1 Scoring Systems

Various scoring systems can be used to identify SCAP and to decide the need for ICU admission (Marti et al. 2012).

The *Pneumonia Severity Index (PSI)* was developed by the investigators of the Pneumonia Outcomes Research Team (PORT) study (Fine et al. 1997). The score classifies the patient into one of five classes based on various patient- and

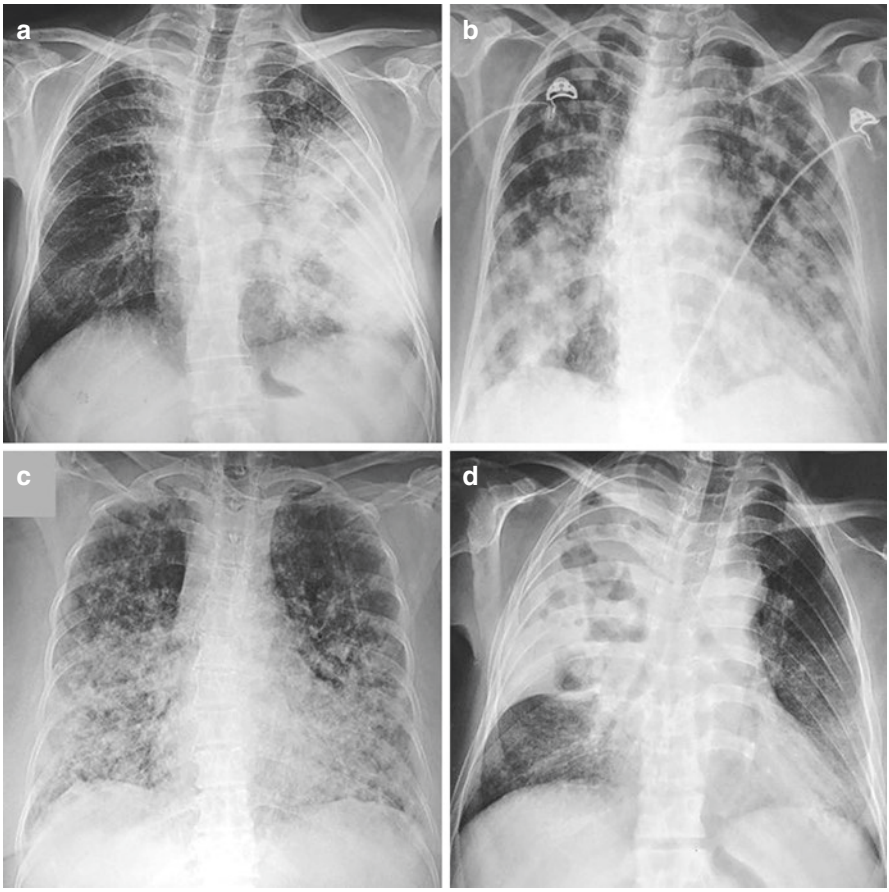


Fig. 4.1 Chest radiographs of patients with severe community-acquired pneumonia. (**a**) Extensive consolidation of left upper and lower lobes. (**b**) Bilateral fluffy airspace opacities suggesting extensive bilateral bronchopneumonia; (**c**) Bilateral alveolar and interstitial opacities in a patient with severe community-acquired pneumonia; (**d**) Extensive consolidation of the right upper lobe with multiple cavitation suggesting necrotizing/cavitary pneumonia

disease-related factors, with each class associated with a different predicted risk for mortality. Points are calculated based on factors such as age, gender, presence of co-morbid medical illness, physical findings, and laboratory and radiographic findings. Patients in classes IV and V have the highest predicted mortality risk of 8.2–9.3% and 27–31%, respectively, and may be considered to signify SCAP. However, PSI has its drawbacks. The score gives disproportionately more weightage to patient-related factors such as age and co-morbidities than to markers specific to the pneumonic illness, per se. Thus, in younger, previously healthy patients, it may underestimate the severity of pneumonia (Niederman et al. 2006). Moreover, pneumonia requiring ICU admission (use of assisted ventilation or vasopressors) does not always translate into higher mortality, and vice versa. Thus, the

Table 4.2 Mimics of community-acquired pneumonia

Inflammatory pathologies	Acute eosinophilic pneumonia
	Alveolar sarcoidosis
	Lupus pneumonitis
	Organizing pneumonia
	ANCA associated vasculitis
	Acute interstitial pneumonia
	Chemical pneumonitis
	Lipoid pneumonia
	Extrapulmonary acute respiratory distress syndrome
	Acute exacerbation of interstitial lung disease
	Acute hypersensitivity pneumonitis
Neoplastic disorders	Bronchogenic carcinoma[a]
	Lymphoma[a]
Iatrogenic	Drug toxicity (like amiodarone, methotrexate, nitrofurantoin, etc.)
	Radiation pneumonitis
Others	Pulmonary edema
	Diffuse alveolar hemorrhage
	Alveolar proteinosis[a]

[a]Usually have an insidious onset and prolonged symptoms

PSI is an excellent predictor of mortality, but it is an inadequate marker to indicate the severity of pneumonia or decide on ICU admission (Niederman 2009; Valencia et al. 2007). Moreover, it is cumbersome to use in routine practice.

CURB-65 is an acronym for the clinical features that are used to assess the pneumonia severity and its prognosis. It assigns 1 point, on a 6-point scale (0–5), each to confusion, blood urea >7 mmol/L (42 mg/dL), respiratory rate ≥30 breaths/min, blood pressure <90 mmHg systolic or ≤60 mmHg diastolic, and age ≥65 years. Mortality increases with increasing score and is >20% with a score of 3 or more. Outpatient treatment is recommended when the score is 0 or 1, in-hospital treatment or hospital-supervised outpatient treatment for a score of 2, and in-hospital treatment is recommended for a score of 3 or more. ICU admission should be considered if the score is 4 or 5. The CURB-65 appears to be more discriminatory compared with the PSI on deciding the place of care and is easier to use. On the contrary, the mortality risk may be underestimated in older patients with co-morbidities, who may decompensate significantly even with mild pneumonia (Niederman 2007).

A simplified *CRB-65* has also been described, which can be used in the emergency department, since it does not require any laboratory parameter and is almost as effective as CURB-65. Since CRB-65 can underestimate the mortality risk slightly, it is advocated for outpatients only (Bauer et al. 2006; Capelastegui et al. 2006). Overall, both these scores may perform similarly in pneumonia patients with low risk of death, while CURB-65 may perform better in patients with a higher risk of mortality (Niederman 2009).

The *IDSA/ATS definition of SCAP* relies on the presence of any of the major criteria (need for invasive mechanical ventilation or septic shock necessitating vasopressors) or any three of the following minor criteria: (1) respiratory rate ≥30 breaths/

min; (2) ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO_2/FiO_2 ratio) ≤250; (3) multilobar infiltrates; (4) confusion/disorientation; (5) blood urea nitrogen level ≥20 mg/dL (equivalent to blood urea ≥43 mg/dL); (6) leukopenia (leucocyte count <4000 cells/mm^3) resulting from infection; (7) thrombocytopenia (<100,000/mm^3); (8) hypothermia (core temperature <36 °C); (9) hypotension requiring aggressive fluid resuscitation (Mandell et al. 2007). Use of non-invasive ventilation can substitute for either of the first two minor criteria. Other criteria that should be considered include acute alcoholism/alcohol withdrawal, cirrhosis, asplenia, hypoglycemia (in nondiabetic patients), unexplained metabolic acidosis or elevated lactate level, and hyponatremia. Several studies have validated the use of these criteria for identifying SCAP (Phua et al. 2009; Liapikou et al. 2009; Chalmers et al. 2011).

Other prognostic scoring systems have also been developed to identify SCAP. Espana et al. have proposed and validated a tool, the CUROX80 for use in the emergency department to predict SCAP or future ICU requirement (Espana et al. 2006). More recent tools have focused on the prediction of the need for intensive respiratory and vasopressor support (IRVS), which is more objective than mere ICU admission, to define SCAP. The *SMART-COP* score was developed to predict the need for IRVS (Charles et al. 2008). The score uses eight parameters that are associated with the need for IRVS. These include systolic blood pressure <90 mmHg, multilobar infiltrates on a chest radiograph, albumin <3.5 g/dL, respiratory rate elevation (≥25/min for those ≤50 years and ≥30/min for those >50 years of age), heart rate >125/min, new onset confusion, hypoxemia (PaO_2 <70 mmHg or SpO_2 ≤93% or PaO_2/FiO_2 <333 for those ≤50 years and PaO_2 <60 mmHg or SpO_2 ≤90% or PaO_2/FiO_2 <250 for those >50 years), and arterial pH <7.35. Low blood pressure, hypoxia, and acidosis are given a score of 2, while the other parameters are given a score of 1 each. Using a cutoff of 3 points, the sensitivity and specificity were 92.3% and 62.3%, respectively, for the need for IRVS with a positive and negative predictive value of 22% and 98.6%, respectively. The performance of the score was superior to that of previously established PSI and CURB-65 scores for predicting the requirement for IRVS (Charles et al. 2008).

Currently, we suggest using the IDSA/ATS definition of SCAP till the time, a better definition or criteria are established. In addition to the indices for severity classification of CAP and prediction of mortality, scores such as the Acute Physiology and Chronic Health Evaluation (APACHE) and the Simplified Acute Physiology Score (SAPS) scores may be used to predict mortality in critically ill patients, in general (Knaus et al. 1985; Le Gall et al. 1993).

4.5.2 Biomarkers

Biomarkers may be used for different purposes in the context of CAP, including diagnosis, determining severity, risk stratification, initiation and discontinuation of antibiotics, and determining prognosis (Sungurlu and Balk 2018). Important biomarkers that have been tested in pneumonia include leucocyte count, C-reactive protein, procalcitonin, soluble triggering receptor expressed on myeloid cells (sTREM), and pro-adrenomedullin (pro-ADM). Amongst these, procalcitonin is the most

tested. However, serum procalcitonin level does not have sufficient specificity, when used alone, for the diagnostic differentiation from alternate diagnoses (for example, pulmonary edema, pulmonary tuberculosis, cryptogenic organizing pneumonia, viral infection, and others) (Yoon et al. 2018; Huang et al. 2014; Ito et al. 2019; Schuetz et al. 2018, 2017). A meta-analysis showed that the area-under the receiver operator characteristic curve was 0.75 for predicting mortality in patients with CAP, which implies that procalcitonin does not have sufficient discriminatory potential (Viasus et al. 2016). Further, a recent pragmatic, multicentric randomized trial showed that the duration of antibiotics is similar with procalcitonin-directed or a guideline-concordant antibiotic regime (Montassier et al. 2019). Serum lactate level, a marker of sepsis, measured at the time of presentation and its subsequent course may have a prognostic role. It may be measured in SCAP to assess the risk of mortality and as one of several parameters guiding initial resuscitation (Chen and Li 2015).

4.5.3 Identification of the Etiologic Agent

Identification of the pathogen causing SCAP is useful in the choice of the antibiotics being administered, and for gathering epidemiologic data in order to formulate or alter the local antibiotic policy. While a rapid test (such as urinary antigen detection) can direct the choice of the initial antibiotic regimen, tests that give a delayed result, such as microbial cultures are helpful in tailoring the antibiotics started empirically.

The IDSA/ATS guidelines recommend that an effort must be made to isolate pathogens in SCAP (Mandell et al. 2007). Pretreatment blood samples for culture and a sputum sample for Gram stain and culture should be obtained. The yield of blood culture is only 5–14% and is reduced to almost half, if the samples are drawn after antibiotic exposure (Rider and Frazee 2018). It has been estimated that for every case of bacteremic pneumococcal pneumonia, there would be about three cases without bacteremia which would be missed on blood culture (Said et al. 2013). Sputum Gram stain test is a sensitive and highly specific test for the identification of the common etiologic agents of CAP in adults (Del Rio-Pertuz et al. 2019). An endotracheal aspirate sample is obtained in place of sputum, in intubated patients. Endotracheal aspirates and bronchoscopic sampling have a higher yield than sputum (Mandell et al. 2007; Gupta et al. 2012; Musher and Thorner 2014). In case of a pleural effusion, a pleural fluid culture must also be performed.

Urinary antigen tests for *Legionella pneumophila* and *S. pneumoniae* should be performed for rapid diagnosis. Serology for other atypical organisms is not routinely indicated (Mandell et al. 2007; Gupta et al. 2012). In the presence of cavitary lesions, testing for *Mycobacterium tuberculosis* (sputum for acid-fast staining and Xpert MTB/RIF) and fungi (Periodic Acid Schiff and Grocott staining) in respiratory samples is also indicated. In case of an endemic or outbreak setting for influenza, a throat swab should be tested using real-time polymerase chain reaction (RT-PCR) for the influenza virus. In the wake of the COVID-19 pandemic, testing for SARS-CoV-2 using RT-PCR in respiratory samples is indicated in suspected cases, in an epidemiological setting. Other than influenza and SARS-CoV-2, routine testing for other viruses using polymerase chain reaction (PCR) in SCAP is generally not useful, outside the research setting (Mandell et al. 2007; Gupta et al. 2012; Musher and Thorner 2014).

4.6 Treatment

4.6.1 General Management

Patients with CAP are initially screened in emergency departments or outpatient clinics. The severity of pneumonia, risk of mortality, and probability of requirement of IRVS must be assessed using the CAP severity scores detailed above. Some patients may warrant a direct admission to the ICU. Others may initially be shifted to the ward, but may later deteriorate despite therapy and may require shifting to the ICU. Hemodynamic support with intensive monitoring and vasopressors/inotropes should be immediately instituted. Similarly, the patient should be quickly assessed for the need for assisted ventilation (high flow nasal cannula, non-invasive ventilation, or invasive ventilation). ARDS should be managed with lung protective ventilation, neuromuscular blockade and, if required, prone positioning. Appropriate fluid resuscitation must be performed in patients with septic shock along with the rational use of appropriate vasopressors/inotropes, blood components, and glucocorticoids, according to standard guidelines (Rhodes et al. 2017). The timely institution of hemodynamic and respiratory support, and administration of appropriate antibiotics have a significant impact on outcomes in SCAP (Phua et al. 2016).

4.6.2 Antimicrobial Therapy

Antibiotic therapy is the mainstay of treatment of CAP. As the causative pathogen is usually unknown at the time of diagnosis (unless a rapid test is positive), the initial choice of antibiotics is empiric. As the most common cause of SCAP is *S. pneumoniae*, the empiric treatment is directed towards this microbe. However, the initial empiric antibiotic therapy should be different in cases with risk factors or clinico-radiological signs of infections with other organisms such as *S. aureus*, *Pseudomonas*, and other GNB. History, physical examination, and radiological appearance may give clues to the etiological agent. Adherence to antibiotic protocols, based on local microbiologic data and prevalent principles of antibiotic stewardship, results in superior outcomes than individualizing therapy (Martin-Loeches et al. 2010; Sakamoto et al. 2017). Thus, the choice of empiric treatment is guided by the presence or absence of risk factors for unusual or resistant pathogens (Table 4.3 and Algorithm 4.1) (Mandell et al. 2007; Gupta et al. 2012).

No Risk for Unusual or Resistant Pathogens Combination therapy with a broad spectrum β-lactam antibiotic (such as amoxicillin-clavulanate, ceftriaxone, cefotaxime) and a macrolide (azithromycin or clarithromycin) is recommended according to standard guidelines (Mandell et al. 2007; Lim et al. 2009). This combination covers the most likely organisms including *S. pneumoniae* and atypical pathogens like *Legionella* and *Mycoplasma*. This combination therapy has been found superior to β-lactam monotherapy, in both pneumococcal and non-pneumococcal SCAP (Baddour et al. 2004; Sligl et al. 2014; Gattarello et al. 2015). Although the IDSA/

Table 4.3 Risk factors for unusual pathogens and drug resistance

Organism	Risk factors
Drug-resistant pneumococcus	Elderly β-lactam or macrolide therapy within 3 months Immunosuppression Alcoholism Day-care centers Medical co-morbidities
Gram-negative bacilli	Recent hospitalization/antibiotics Cardiopulmonary co-morbidities Smoking/alcoholism Underlying malignancy
Community-acquired methicillin resistant *Staphylococcus aureus*	Elderly End-stage renal disease/renal replacement therapy Prior MRSA infection/colonization Recent hospitalization/antibiotics (particularly fluoroquinolones) Contact sports Men who have sex with men Medical co-morbidities
Pseudomonas spp	Chronic obstructive pulmonary disease Structural lung disease like bronchiectasis Immunosuppression/recent steroid exposure Recent antibiotics/recent hospitalization

ATS guidelines recommend that a respiratory fluoroquinolone (levofloxacin or moxifloxacin) may be used instead of a macrolide, fluoroquinolone use is not recommended in regions endemic for tuberculosis (Mandell et al. 2007; Gupta et al. 2012). Moreover, observational studies have suggested that regimens containing macrolides may have superior outcomes compared to fluoroquinolones, possibly due to their immunomodulatory properties (Martin-Loeches et al. 2010; Metersky et al. 2007; Restrepo et al. 2009; Lee et al. 2017). Initiation with parenteral treatment is recommended for SCAP (Lim et al. 2009).

If there are risk factors for or suspicion of unusual pathogens, the empiric antimicrobial therapy should be modified accordingly:

Risk Factors for *Pseudomonas aeruginosa* and Other GNB A prior infection/colonization with *Pseudomonas*, prior tracheostomy, structural lung diseases (like bronchiectasis and severe COPD), and immunosuppression (including repeated or chronic glucocorticoid use) have been implicated as risk factors for infection with *Pseudomonas aeruginosa* (Mandell et al. 2007; Cilloniz et al. 2019, 2016b; Restrepo et al. 2018; Sibila et al. 2015). Exposure to antibiotics in the recent past additionally predicts infection with drug-resistant *P. aeruginosa* (Cilloniz et al. 2016b). If risk factors for *Pseudomonas* CAP are present, an anti-pseudomonal β-lactam antibiotic (piperacillin-tazobactam, cefoperazone, cefoperazone-sulbactam, ceftazidime, cefepime, or a carbapenem) must be considered for the initial treatment in combina-

tion with either a fluoroquinolone or macrolide (for atypical organisms) (Mandell et al. 2007; Gupta et al. 2012; Rider and Frazee 2018). As risk factors for *Pseudomonas* and other GNB overlap, the same antibiotics should be utilized, if such risk factors are present or GNB is detected on gram staining, until the culture results confirm non-pseudomonal GNB. This strategy has been shown to reduce the risk of inappropriate empiric therapy (Mandell et al. 2007). If a non-pseudomonal GNB is confirmed, treatment can be tailored according to the sensitivity profile. Most such pathogens can be treated with a cephalosporin like cefuroxime, cefotaxime or ceftriaxone, β-Lactam/β-lactamase inhibitor, fluoroquinolone, or carbapenem (Lim et al. 2009).

Risk Factors for *Staphylococcus aureus* If there is a strong clinical suspicion of *Staphylococcus aureus* infection in SCAP, due to the presence of risk factors (Table 4.3), or if there is cavitary pneumonia or empyema, addition of vancomycin or teicoplanin must be considered until the results of culture are available (Rubinstein et al. 2008). Linezolid can also be used, but in countries with high burden of tuberculosis including India, empiric use of linezolid is discouraged (Gupta et al. 2012). Once the organism has been isolated and if found methicillin-sensitive (MSSA), the antibiotic should be changed to cloxacillin, oxacillin, or nafcillin (Rubinstein et al. 2008).

Suspicion of Influenza or COVD-19 During a pandemic/epidemic of influenza or the influenza season, a high index of suspicion should be kept for influenza pneumonia, especially in the presence of nasal discharge, sore throat with diffuse ground glass opacification, or infiltrates on chest radiograph. It may or may not be associated with a secondary bacterial infection. Antiviral therapy with oseltamivir or zanamivir is warranted, preferably within 24 h, along with antibacterial therapy as per the local guidelines (Fiore et al. 2011). Since 2019, coronavirus disease caused by SARS-CoV-2 has also become an important diagnostic consideration in SCAP.

Other Factors Affecting the Choice of Antibiotics The empiric regimen will also be guided by the results of sputum or pleural fluid Gram stain report, which can usually be obtained in a few hours, the presence of renal or hepatic dysfunction, recent exposure to antibiotics, and known drug allergies. In case of penicillin allergy, β-lactams (including cephalosporins) should be avoided and aztreonam can be used.

Timing of Initiation of Antibiotics It is recommended that antibiotics should be initiated as early as the diagnosis of SCAP is made, preferably within 4 h, and ideally within 1 h (Mandell et al. 2007; Gupta et al. 2012; Rider and Frazee 2018). Time to first antibiotic dose may affect the outcome in SCAP, especially if the patient has sepsis or septic shock (Daniel et al. 2016; Houck et al. 2004; Lee et al. 2016).

Route and Doses Initiation with parenteral route is recommended for SCAP due to variable absorption via the oral route (Lim et al. 2009). Maximal doses should be used to ensure attainment of drug levels above the minimum inhibitory concentra-

tion (MIC). Pharmacokinetic and pharmacodynamic aspects must also be taken into consideration. β-lactams should ideally be given as extended infusions, whereas azithromycin, aminoglycosides, and fluoroquinolones must be used as once daily bolus dosing (Table 4.4).

Change of Antibiotics After Results of Cultures The combined yield of cultures of blood and respiratory samples cultures in CAP is universally low and only about a quarter to one-third CAP patients can be microbiologically defined in the therapeutic time-frame (Lim et al. 2009). It has also been observed that results of blood culture prompt a change in antibiotic prescription in a very small number of cases (Afshar et al. 2009; Campbell et al. 2003; Kennedy et al. 2005). Empirical antibiotic approach and pathogen-directed antibiotic approach have been shown to have similar efficacy. However, the latter approach has lesser adverse effects and may theoretically reduce the emergence of drug-resistant microorganisms (van der Eerden et al. 2005). It is thus recommended that if the culture results identify a definite pathogen, antimicrobial therapy must be narrowed to a pathogen-directed specific therapy (Lim et al. 2009). The choice of therapy should be based on results of in vitro susceptibility or local antibiotic policies based on sensitivity patterns. For example, amoxicillin,

Table 4.4 Daily dosing and schedule of common antibiotics in SCAP

Antibiotic	Dose
Ceftriaxone	2 g IV q12h (1-h infusion)
Cefotaxime	1 g IV q8h (1-h infusion)
Amoxicillin-clavulanate	1.2 g IV q8h (1-h infusion)
Azithromycin	500 mg IV q24h (1-h infusion)
Clarithromycin	500 mg IV q12h (1-h infusion)
Anti-pseudomonal beta-lactams	
Piperacillin-tazobactam	4.5 g IV q6h (4-h infusion)
Cefoperazone-sulbactam	2 g IV q12h (3-h infusion)
Ceftazidime	2 g IV q8h (3-h infusion)
Cefepime	2 g IV q8h (3-h infusion)
Anti-pseudomonal aminoglycosides	
Amikacin	15–20 mg/kg IV q24h (1-h infusion)
Gentamicin	5–7 mg/kg IV q24h (1-h infusion)
Tobramycin	5–7 mg/kg IV q24h (1-h infusion)
Anti-pseudomonal fluoroquinolones	
Ciprofloxacin	400 mg IV q8h (1-h infusion)
Levofloxacin	750 mg IV q24h (1-h infusion)
Carbapenems	
Imipenem	1 g IV q8h (2-h infusion)
Meropenem	1 g IV q8h (3-h infusion)
Anti-MRSA drugs	
Vancomycin	500 mg IV q6h (4-h infusion)
Teicoplanin	12 mg/kg loading dose followed by 6 mg/kg IV q24h (4-h infusion)
Linezolid	600 mg IV q12h (1-h infusion)
Clindamycin	600 mg IV q8h (1-h infusion)

clarithromycin, cefuroxime, ceftriaxone, or cefotaxime may be chosen if *S. pneumoniae* is isolated. Similarly, fluoroquinolones or macrolides are appropriate choices for *Legionella* species (Lim et al. 2009). If CA-MRSA is identified, clindamycin, trimethoprim/sulfamethoxazole, rifampicin, vancomycin, or linezolid may be chosen based on sensitivity pattern and inducible resistance (in case of clindamycin) (Lim et al. 2009; Liapikou et al. 2014). It must be re-iterated here that 11% cases of CAP will have mixed infections (Cilloniz et al. 2016a, 2011). However, the co-pathogens in most such instances would be viruses and hence tailoring of the antibiotic therapy can be safely carried out (Lim et al. 2009).

Failure of Response to Initial Therapy Clinical response to appropriate antimicrobial therapy in terms of improvement in fever, tachycardia, confusion, and hypotension usually occurs within 2–4 days (Halm et al. 1998; Menendez et al. 2004a). However, rate of resolution also depends on age and co-morbid conditions (Low et al. 2005). Failure to achieve adequate response or clinical/radiological worsening after initial therapy may occur in about 15% cases of CAP of which most failures occur in the first 72 h (Menendez et al. 2004b). In SCAP managed in ICU, failure rate may be as high as 40% and is responsible for significant increase in mortality (Sligl and Marrie 2013; Morgan and Glossop 2015). The most common cause of treatment failure is an inadequate host response to infection, rather than inappropriate therapy (Sligl and Marrie 2013). Higher severity score of pneumonia, multilobar infiltrates, cavitation, pleural effusion, leukopenia, and presence of comorbidities are associated with treatment failures (Low et al. 2005; Menendez et al. 2004b; Roson et al. 2004). Among specific etiologic microorganisms, *Legionella pneumophila* and gram-negative pathogens are associated with a higher incidence of treatment failures (Low et al. 2005; Roson et al. 2004). Various factors that must be considered when there is a perceived failure of the initial therapy are mentioned below.

a. *Incorrect diagnosis*—Almost 16% of treatment failures are due to non-infective causes (Menendez et al. 2004b). Inflammatory disorders like vasculitis, organizing pneumonia, eosinophilic pneumonia, and other non-infective interstitial pneumonia may sometimes mimic CAP. Also, heart failure, alveolar hemorrhage and, less commonly, neoplasms can sometimes mimic CAP (Low et al. 2005). In such cases, detailed clinical evaluation, and advanced imaging modalities like computed tomography, when feasible, with or without percutaneous or bronchoscopic sampling may lead to a revision of the diagnosis.
b. *Targeting incorrect pathogen*—Uncommon presentations of tuberculosis, fungal pneumonia, or *Pneumocystis* pneumonia can lead to inappropriate therapy if managed empirically as CAP (Low et al. 2005). Pneumonia due to viral infections like influenza; or, severe acute respiratory syndrome, Middle East Respiratory Syndrome, or COVID-19 all caused by different coronaviruses may lead to progressive pneumonia and treatment failure (Low et al. 2005). Also, secondary nosocomial infection may occasionally lead to late treatment failure (after 72 h) (Genne et al. 2003). Also, in the presence of uncontrolled blood sugar with or without acidosis, neutropenia, or prior use of high-dose systemic glucocorticoids, a possibility of invasive fungal infection such as aspergillosis or mucormycosis should be considered.

c. *Drug-resistant pathogens*—Drug-resistant organisms account for only about 6% of treatment failures, if guideline-concordant antibiotic policy is used in initial therapy (Menendez et al. 2004b; Genne et al. 2003). It is important, therefore, that antibiotic policy adapted in a particular ICU is guided by the local antibiotic susceptibility data.
d. *Patient-related factors*—Decompensation of underlying co-morbid illness may lead to both early and late treatment failure (Sligl and Marrie 2013). Also, mechanical factors like an obstructed bronchus due to a mass or sequestration may lead to a poor response to antimicrobial therapy (Low et al. 2005).
e. *Complications of SCAP and adverse effects of therapy*—These are usually responsible for late failures and include ARDS, undrained empyema, lung abscess, and metastatic pyogenic abscesses (Sligl and Marrie 2013). In an analysis of treatment failures in patients recruited in 16 CAP trials, 30% of perceived treatment failures were because of adverse effects of antibiotics (Genne et al. 2003).

It is recommended that on perceived failure of initial antimicrobial therapy and once non-infective causes of the same are excluded (as elucidated above), microbiological analysis should be reviewed and repeated to rule out unusual organisms and mixed infections (Lim et al. 2009). However, a definite cause of treatment failure is elusive in nearly half of the failures (Menendez et al. 2004b; Genne et al. 2003). In the absence of definite microbiological data to guide therapy, addition of a fluoroquinolone (to β-lactam-macrolide combination) and/or vancomycin, and bronchoscopic sampling may be considered (Lim et al. 2009). Similarly, computed tomography scan of the chest or pleurocentesis may be carried out where indicated (Sligl and Marrie 2013).

Duration of Antibiotics Most patients of SCAP do not require treatment for more than 5–7 days. If azithromycin is used as the macrolide, a 3-day course of 500 mg/day is usually sufficient. If the patient has attained clinical stability and has remained afebrile for 2–3 days, antibiotics can be stopped in 5–7 days (Mandell et al. 2007; Gupta et al. 2012; Tansarli and Mylonakis 2018; Uranga et al. 2016). Procalcitonin levels <0.25 ng/ml or greater than 80% decline from the peak value can also be used to discontinue antibiotic therapy. However, procalcitonin levels should be interpreted together with clinical course, and not in isolation (Schuetz et al. 2018, 2017).

Pathogens such as *Pseudomonas* and *Legionella* may require 7–10 days of therapy and often longer, depending on the clinical response. Uncomplicated MRSA CAP may be treated with 7–10 days of antibiotics, but longer treatment may be required when there is bacteremia (2 weeks) or metastatic infections (4–6 weeks) (Mandell et al. 2007; Gupta et al. 2012; Tansarli and Mylonakis 2018; Uranga et al. 2016). Despite achieving clinical stability and a decline in procalcitonin levels, prolonged antibiotic therapy may be required in lung abscess, empyema, or necrotizing pneumonia or if extrapulmonary infections like endocarditis or meningitis are detected (4–6 weeks).

4.6.3 Adjunctive Therapies

Glucocorticoids In the last decade there have been several studies on the use of adjunctive glucocorticoids in SCAP, with the premise that exaggerated inflammation increases the mortality and morbidity in SCAP (Blum et al. 2015; Tagami et al. 2015; Torres et al. 2015). Use of anti-inflammatory glucocorticoids along with appropriate antibiotics may lead to improved outcomes. At present, however, the evidence is conflicting, and the routine use of glucocorticoids cannot be recommended.

A systematic review and meta-analysis involving nine randomized controlled trials and six cohort studies till 2015 concluded that use of glucocorticoids in CAP was safe, reduced the duration of illness, and prevented progression to ARDS (Wan et al. 2016). A Cochrane analysis published subsequently concluded that glucocorticoids have a mortality benefit in SCAP but not in non-severe CAP. The numbers needed to treat (NNT) was 18 patients to prevent one death from SCAP (Stern et al. 2017). More recently, one systematic review and individual patient data meta-analysis found that glucocorticoids reduced time to clinical stability and length of hospitalization without any mortality benefit and at the cost of increased risk of CAP related rehospitalization and hyperglycemia (Briel et al. 2018). In contrast, another recently published meta-analysis focused on glucocorticoids use in SCAP showed mortality benefit and reduced hospital stay with the use of glucocorticoids (Wu et al. 2018).

Overall, it appears that glucocorticoids may have a role in the management of SCAP to hasten recovery, but further studies will be required to identify the characteristics of patients in whom the benefits will outweigh the risks and also to establish the timing, dose, and duration. A large ongoing trial—ESCAPe trial (Extended Steroid in CAP(e); ClinicalTrials.gov NCT01283009) is likely to answer some of these questions.

Other Systemic Adjunctive Therapies Intravenous Immunoglobulin (IVIg) in general and IgM, in particular, have a vital role in host defense mechanisms in SCAP. IVIg preparations, specially, IgM-enriched formulations have been studied for their potential role as an adjunctive therapy in SCAP, with less than promising results (Garnacho-Montero et al. 2018). A recently concluded phase II trial failed to show benefit of IgM-enriched IVIg therapy in mechanically ventilated SCAP patients (Welte et al. 2018). Post-hoc analysis suggested that a few subgroup populations may benefit from such therapy.

Statins may be potential candidates for adjunctive therapy in SCAP due to their anti-inflammatory and antioxidant properties. However, prospective trials have found no role of statins in improving the outcomes in SCAP and cannot be recommended at present (Havers et al. 2016; Viasus et al. 2015).

Chest Physiotherapy There is no role of routine chest physiotherapy in all patients with SCAP. Hospital-based physiotherapy, after achieving clinical stability, may be useful in elderly patients admitted with CAP, who have declining physical function and difficulty in clearing respiratory secretions. It may reduce the re-admission rates and should be encouraged (Sun Jung Kim et al. 2015).

4.6.4 Management of Parapneumonic Effusion

In every case of SCAP, pleurocentesis should be carried out if significant pleural effusion is present on imaging (Skouras et al. 2010). Loculated effusions and presence of enhancing thickened parietal pleura on CT portend a poor prognosis and must be subjected to diagnostic thoracentesis, even if small in size (Colice et al. 2000). If the fluid is frank pus or/and has positive gram stain or culture, intercostal chest drainage must be done. Other indications for the same are an effusion occupying greater than half of the hemithorax, loculated effusion, effusion with thickened parietal pleura, pleural fluid glucose less than 60 mg/dL, or pH less than 7.2 (Colice et al. 2000). A few patients with loculated effusions may require intrapleural fibrinolytics, thoracoscopic adhesiolysis, or surgical decortication (Ferreiro et al. 2018; Dhooria et al. 2014).

4.6.5 Assessing Response to Treatment

With appropriate treatment, clinical response should be achieved in 2–3 days, especially improvement in fever, hypotension, oxygenation, tachycardia, and tachypnea. Cough and fatigue may take up to 2 weeks to resolve and resolution of radiological infiltrates may lag behind by a month or more. Radiological resolution may be delayed particularly in the elderly, in those with multilobar presentation at presentation and in those with underlying structural lung disease. However, a lack of clinical response by the third day of treatment indicates a possibility of either an inappropriate antibiotic or sometimes an incorrect diagnosis, as discussed earlier (Halm et al. 1998; Menendez et al. 2004a; Bruns et al. 2007; Morley et al. 2017). Routine chest radiograph during the course in hospital is not warranted if the patient is clinically improving (Bruns et al. 2007).

When the patient is hemodynamically stable and has a functional gastro-intestinal tract, switch-over must be made to appropriate oral antibiotics (Gupta et al. 2012; Oosterheert et al. 2006). The choice of oral antibiotic can be deduced directly from the intravenous combination to which the patient has responded, if an effective oral formulation is available (Mandell et al. 2007). In case of intravenous cephalosporins, however, a switch to oral amoxicillin-clavulanate is preferred (Lim et al. 2009). Narrowing to monotherapy can be considered if culture results have not shown polymicrobial infection (Mandell et al. 2007; Lim et al. 2009).

4.6.6 Discharge

Patients can be discharged once they have been switched to oral antibiotics, have attained clinical stability, and have an unequivocally improving clinical course. Follow-up must be done after a week, on an outpatient basis. A chest radiograph must be performed after 2–3 months to look for any underlying lung disease, especially in the elderly and in smokers.

At the time of discharge of patients with SCAP, the status of pneumococcal and influenza vaccination must be enquired, and those not immunized must be advised to do so, as per the local guidelines. Smoking cessation must be re-iterated at this point and optimization of other medical illnesses must be ensured with advice on regular medical follow-up for each of those illnesses. Even after discharge, the mortality of SCAP patients remains higher than controls at the end of 1 year and 2 years, even when they have no co-morbidities. Cardiovascular risk may remain high even up to 5–10 years and therefore appropriate therapy must be resorted to reduce the risk, like institution of antiplatelet or statin therapy, when eligible (Rider and Frazee 2018).

4.6.7 Prevention of SCAP

Pneumococcal Vaccination There are two kinds of pneumococcal vaccines currently available: 23-valent pneumococcal polysaccharide vaccine (PPV23) and 13-valent pneumococcal conjugate vaccine PCV13 (van Werkhoven and Huijts 2018). PPV23 has been shown to prevent invasive pneumococcal disease in all age groups except those less than 2 years of age but its efficacy to prevent pneumonia has not been conclusively established in elderly patients and those with chronic co-morbid condition (van Werkhoven and Huijts 2018). On the other hand, PCV13 has demonstrated efficacy to prevent vaccine-type invasive disease as well as pneumonia in immunocompetent elderly patients.

Influenza Vaccination Influenza vaccines are available as trivalent/quadrivalent inactivated, quadrivalent live-attenuated, and quadrivalent recombinant vaccines (Grohskopf et al. 2018). Efficiency of influenza vaccines to prevent pneumonia or hospitalization has varied from 25% to 53% in various meta-analyses (Heo et al. 2018). The vaccine preparations are updated annually based on the prevalent strains (Grohskopf et al. 2018). Currently, in India, annual vaccination with influenza vaccine is recommended for all individuals with co-morbid conditions, immunocompromised patients (only inactivated vaccine), pregnant women, and health care workers. Vaccination is desirable for elderly individuals (≥65 years) and children between ages of 6 months and 8 years (Ministry of Health and Family Welfare Directorate General of Health Services (National Centre for Disease Control) 2018).

4.7 Future Directions

Biomarkers Presepsin is the soluble fragment of CD14 (monocyte lipopolysaccharide receptor). Levels of presepsin correlate with increased bacterial phagocytosis and correlate with development of sepsis and shock (Klouche et al. 2016). Fatty acid binding proteins (FABP) have been found to help in predicting the severity, risk stratification, and assessment of the response to treatment effectively, when

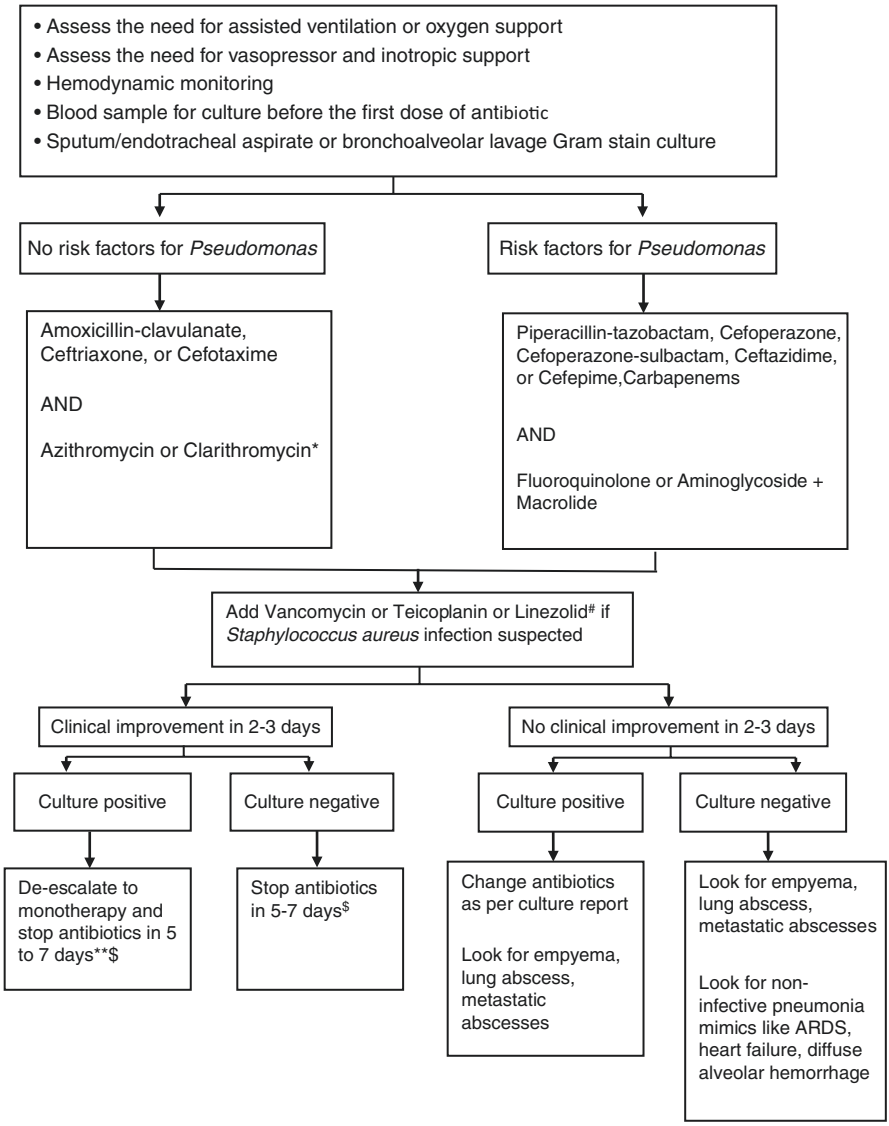
measured in serum or urine (Chen and Li 2014; Tsao et al. 2016). Adrenomedullin (ADM) and its product mid-regional-pro ADM have been studied as markers of severity of CAP and its outcome with some promising results (Leoni and Rello 2017; Elke et al. 2018; Pereira et al. 2006). Expression of monocyte human leukocyte antigen-DR (mHLA-DR) on monocyte membranes, 24 h after admission in SCAP patients, is lower in individuals who are not likely to survive by day 28 (Zhuang et al. 2015). These novel biomarkers probably indicate the virulence of the pathogen, but more importantly, they signify the dysregulated immune response of the host and other unknown host characteristics that are associated with the development of severe pneumonia (Leoni and Rello 2017).

Detection of Pathogens Conventional culture and serological methods have a high turnaround time and lack sensitivity and specificity, thus leading to dependence on appropriate empiric treatment. A large number of SCAP are due to viruses as expounded earlier, implying that a lot of unnecessary antibiotic use is in practice. Novel molecular techniques like multiplex real-time PCR can reduce the turnaround time and improve the detection accuracy in identifying the causative pathogens in SCAP (Gelfer et al. 2015). Also, there is a difference in the genetic expression of host in non-infective inflammation, bacterial infection, and viral infection. An understanding and detection of the same may avoid the overuse of antibiotics (Sweeney et al. 2016).

Personalized Treatment Apart from the virulence of pathogens and immunity of the host, there are probably several other factors that predict progression to dysregulated immunity, development of SCAP, and poor response to treatment. These might include the inherent metabolic processes of the host and the way they get affected during an infection. Metabolomics is an emerging branch that deals with these aspects. Using liquid chromatography tandem mass spectrometry, a host of metabolites, particularly lipid metabolites, have been identified that may serve as biomarkers of SCAP and may predict development of sepsis and poor outcome (Neugebauer et al. 2016; To et al. 2016). Similarly, sick-euthyroid syndrome characterized by low levels of free triiodothyronine (FT3) with low to normal levels of other thyroid hormones has been associated with poor outcomes in CAP suggesting a possible maladaptive response (Liu et al. 2016). Genetic factors also probably have a role and individual genetic polymorphisms may dictate not only susceptibility to severe infection but also response to treatment. In a recent genome-wide association studies in patients admitted to ICU with pneumonia and sepsis, several single nucleotide polymorphisms were identified on FER gene on chromosome 5, that were strongly associated with clinical outcomes (Rautanen et al. 2015). Defects in transcriptional signatures pertaining to immunological and inflammatory response have been studied in the blood transcriptome of SCAP patients (Hopp et al. 2018). Besides, the intrinsic pulmonary flora of the host, as judged by microbiota profiles of sputum/other respiratory samples, may predict the severity of CAP, length of stay, and outcome (Pettigrew et al. 2016). Developments are underway in the fields of vaccination, immunomodulation, use of monoclonal antibodies against pathogens and their

toxins, and use of nanotechnology for intensifying the attack on pathogens (Rello and Perez 2016). Hence, metabolomics, genomics, microbiomics, transcriptomics, and immunology are the way forward in our understanding of SCAP. They may lead to the development of valuable biomarkers and targeted treatment strategies paving way for personalized management in SCAP.

Algorithm 4.1 Approach to Management of SCAP



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Ventilator Associated Pneumonia

5

Saurabh Mittal and Karan Madan

Key Points

- Ventilator associated pneumonia is pneumonia occurring in an individual on mechanical ventilation for more than 48 h.
- Endotracheal tube placement leads to loss of protective mechanisms predisposing the patient to development of pneumonia.
- Though predominant organisms include gram negative bacilli such as Acinetobacter, Pseudomonas and Klebsiella, gram positive organism methicillin resistant *Staphylococcus aureus* is also an important disease-causing pathogen.
- Diagnosis is based upon clinical features and is supported by radiograph and respiratory secretions culture.
- Empirical treatment depends upon various risk factors and usually include a combination of antibiotic regimen covering gram negative as well as gram positive organisms.
- Prevention of VAP remains the most important strategy and hand hygiene plays a dominant role in prevention of this disease.

5.1 Introduction

Infections in ICU is a common occurrence likely due to patients' vulnerability due to their illness and prevalence of various virulent organisms. The common sites involved in ICU infections include lung, urinary tract, skin, paranasal sinuses and oral cavity though most common site remains lung. Ventilator associated

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pneumonia (VAP) is an important entity to be understood by all physicians dealing with critically ill patients as it has a major impact on patient outcomes.

VAP is defined as pneumonia occurring in patients after 48 h of endotracheal intubation. It is an important subset of hospital acquired pneumonia (HAP) patients. Early onset VAP is defined as occurring within 4 days and is usually caused by sensitive organisms while late onset VAP (occurring on day 5 or after) is associated with multidrug-resistant (MDR) pathogens and is associated with a worse prognosis. Most often VAP is caused by bacteria but it may occur because of fungal pathogens as well as viruses during viral epidemics.

Despite major advances in ICU care, VAP continues to remain a nightmare for intensivists and it leads to increased treatment costs, increased hospital and ICU stay as well as increased mortality. To implement preventive strategies for the same should be the aim of all ICU services. The management of VAP centres around early diagnosis and effective treatment for appropriate duration.

5.2 Epidemiology and Risk Factors

The exact incidence of VAP depends on the definitions used and the population studied. The maximum risk of VAP is in early in the course of ICU stay. VAP affects around 9–27% of all intubated patients and its incidence increases with increasing duration of mechanical ventilation. The risk is about 3% per day during first 5 days, 2% per day during fifth to tenth day and 1% per day thereafter. As duration of mechanical ventilation is short for most patients, the maximum cases of VAP occur within 4 days of mechanical ventilation. About 35% to 70% of ARDS (acute respiratory distress syndrome) patients develop VAP. Independent predictors of VAP include a primary diagnosis of trauma/CNS/respiratory/cardiac illness, witnessed aspiration and use of paralytic agents. Other risk factors for VAP are diabetes, alcoholism, hypotension, azotemia, enteral feedings, surgery, supine position, malignancy and severe illness (APACHE >18). Older age of the patient and presence of co-morbidities increase incidence of VAP as well as lead to poor outcome. Presence of co-morbidities predisposes patients to specific organism as well such as *H. influenzae* and pneumococcus in COPD, Pseudomonas and *S. aureus* in bronchiectasis and MRSA in diabetics and alcoholics. Inappropriate antibiotic therapy, steroid use, sedatives and excessive use of antacids and proton pump inhibitors predispose patients to VAP. Routine change of ventilator circuits, use of nebulizers, bronchoscopes and endoscopes are also associated with increased risk of VAP.

VAP is usually linked to aspiration of oropharnygeal and/or oesophageal contents, direct inoculation of lower airways during intubation, infected aerosol inhalation, infection through biofilms which form on endotracheal tube and haematogenous spread.

Pharmacologic interventions in form of concurrent steroid therapy, sedatives, and use of gastroprotective agents lead to increased risk of VAP. Inappropriate use of antimicrobials leads to selection of MDR pathogens causing difficult-to-treat infections. Risk factors for MDR pathogens are shown in Table 5.1.

Table 5.1 Risk factors for MDR pathogens

Antimicrobial use in previous 90 days
Current hospitalization for more than 5 days
Hospitalization for more than 2 days in the last 90 days
High prevalence of antibiotic resistance in hospital
Resident of nursing home
Chronic dialysis
Immunosuppressive therapy

Table 5.2 Common organisms causing VAP

Gram negative aerobes
Pseudomonas aeruginosa *Klebsiella pneumoniae* Acinetobacter sp. *Escherichia coli* Enterobacter sp. Serratia Proteus sp.
Gram positive aerobes
Staphylococcus aureus *Streptococcus pneumoniae*
Gram negative anaerobes
Bacteroides fragilis
Others
Candida albicans Influenza virus

Patients with VAP have two to tenfold higher risk of death, though attributable mortality to VAP is unclear as it is difficult to determine the role of VAP in patients dying with severe illnesses.

The various pathogens causing VAP are enlisted in Table 5.2. The most common organisms remain gram negative bacilli including *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, Acinetobacter and *E. coli*. Gram positive organisms like MRSA have also emerged as a challenge. Polymicrobial infections are also common.

5.3 Pathophysiology

The respiratory tract has many protective mechanisms including anatomic barriers, cough reflex, mucociliary clearance mechanisms and innate and humoral immune factors. Due to placement of endotracheal tube, and poor sensorium and sedation, these mechanisms are lost. It often involves colonization of aerodigestive tract with pathogenic organisms, aspiration of contaminated secretions, colonization of lower airways and then leading to invasive infection. Endotracheal tube facilitates the entry of bacteria into lower airways by pooling and leakage of secretions from subglottic area through small channels formed around ET cuff. Biofilm formation on ET and patient's position also have an important influence on VAP occurrence.

5.4 Approach to the Patient

The early diagnosis of VAP requires a high clinical suspicion and timely evaluation. But all worsening in ICU patients should not be attributed to VAP. The gold standard for the diagnosis of VAP is still lacking. Usually clinical features including patient's symptoms in form of fever, new chest examination findings, radiographic changes and hematologic parameters are taken into consideration to start empirical antibiotics but reliance on only these parameters usually leads to over-treatment. Current American Thoracic Society (ATS) guidelines recommend microbiologic sampling of lower airways in form of semi-quantitative or quantitative cultures of non-bronchoscopic lavage (mini-BAL), broncho-alveolar lavage (BAL) or protected specimen brush (PSB).

5.5 Clinical Diagnosis

There are few definitions which have been proposed as the diagnostic criteria for VAP. Among these the definitions suggested by ACCP (American College of Chest Physicians) and CDC (Centers for Disease Control and Prevention) are widely used. Their description is given below:

ACCP Definition A diagnosis of pneumonia is defined as the presence of new, persistent pulmonary infiltrates not otherwise explained, appearing on chest radiographs. Moreover, at least two of the following criteria are required:

1. Temperature of >38 °C.
2. Leukocytosis >10,000 cells/mm^3.
3. Purulent respiratory secretions.

A pneumonia is ventilator associated when it occurred after intubation and was judged not to have incubated before an artificial airway is put in place.

CDC Definition Radiological:

Two or more serial chest radiographs with at least one of the following:

1. New or progressive and persistent infiltration.
2. Consolidation.
3. Cavitation

For any patient, at least one of the following:

1. Fever (>38 °C or 100.4 °F) with no other recognized cause.
2. Leucopenia (<4000 WBC/mm3) or leukocytosis (>12,000 WBC/mm^3).
3. For adult ≥70 years old, altered mental status with no other recognized cause.

Table 5.3 Clinical pulmonary infection score

	Points		
Variable	0	1	2
Temperature (°C)	≥36.1 to ≤38.4	≥38.5 to ≤38.9	≥39 or ≤36
WBC count (cells)/uL	≥4000 to ≤11,000	<4000 to >11,000	
Secretions	Absent	Present, nonpurulent	Present, purulent
PaO_2/FiO_2	>240 or ARDS		≤240 and no ARDS
Chest radiography	No infiltrate	Diffuse or patchy infiltrate	Localized infiltrate
Microbiology	No or light growth	Moderate or heavy growth	

And at least two of the following:

1. New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions.
2. New onset or worsening of cough, or dyspnoea or tachypnoea.
3. Rales or bronchial breath sounds.
4. Worsening gas exchange (e.g. oxygen desaturation (e.g. $PaO_2/FiO_2 \leq 240$), increased oxygen requirement, or increased ventilator demand).

Some clinicians emphasize a weighted approach for clinical diagnosis of VAP. The Clinical Pulmonary Infection Score (CPIS) is an example of this approach. It includes six parameters assessment and each is scored from 0 to 2. A score of 6 or more is considered predictive (not diagnostic) of VAP. It should be performed at initiation of antibiotic therapy and then serially after 2–3 days to assess its effectiveness and de-escalation of antibiotics. Table 5.3 shows various parameters and scoring system in CPIS.

In ICU, all radiologic infiltrates do not support a diagnosis of VAP. Pneumonia accounts only for one-third of all pulmonary infiltrates in ICU. The noninfectious causes include pulmonary oedema, ARDS, atelectasis and effusion. The quality of portable X-rays in ICU is almost always suboptimal for complete assessment predominantly due to patient position, soft tissue oedema and presence of various wires and catheters obscuring the view.

The National Healthcare Safety Network has recently published a new algorithm for the diagnosis of VAP independent of radiological findings as shown in Fig. 5.1. It is yet to be validated but it has led to new insights into diagnosis of VAP.

5.6 Microbiologic Diagnosis

Many clinicians believe that microbiologic diagnosis is necessary for VAP to optimize the antimicrobial therapy. Many studies have shown that obtaining respiratory specimen for cultures from lower respiratory tract using bronchoscopic or non-bronchoscopic methods can improve diagnostic yield and facilitate appropriate treatment.

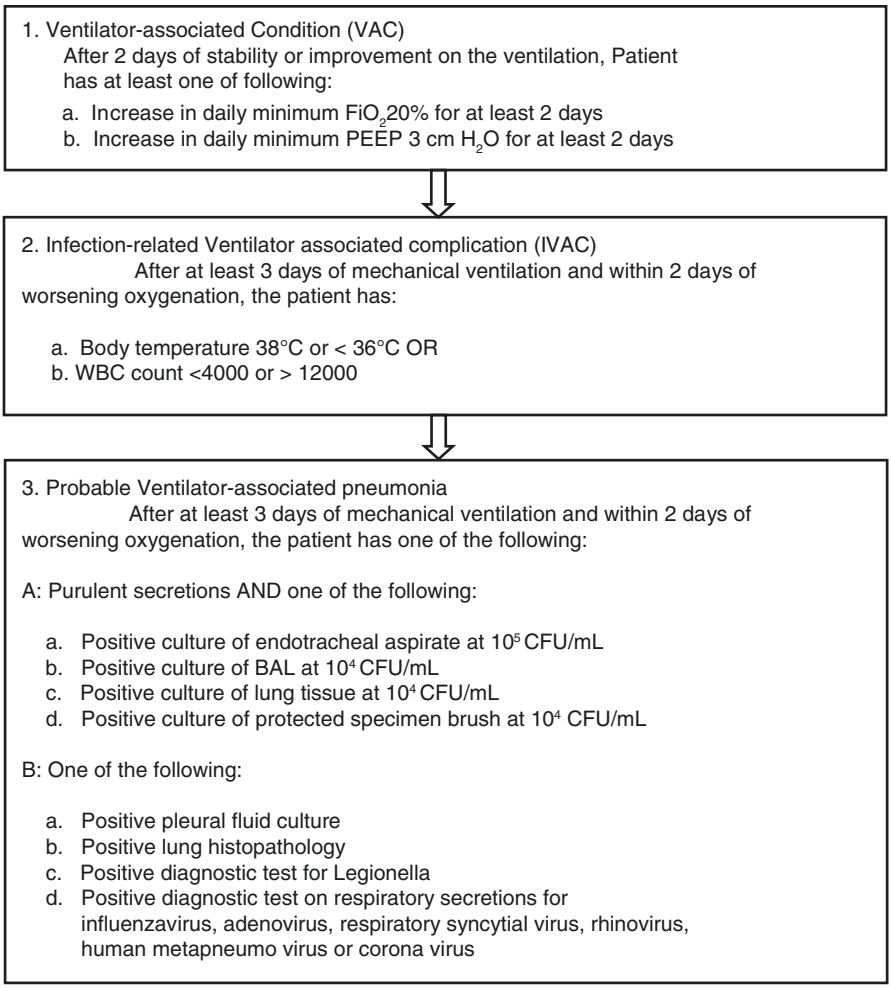

Fig. 5.1 NHSN algorithm for diagnosis of VAP

Using fibreoptic bronchoscope, we can visualize lower airways and obtain samples in form of BAL and protected specimen brush. The selection of appropriate site for sampling is usually based on radiological involvement but in case of diffuse infiltrates samples should be obtained from area with maximum endobronchial abnormality. These samples should be sent for quantitative cultures. Quantitative cultures of BAL and/or PSB specimens consistently yield fewer microorganisms above the diagnostic threshold than are present in qualitative cultures of tracheal aspirates. Thus, when therapeutic decisions are based on these data, fewer patients are treated with antibiotics and a potentially narrower spectrum of therapy is used than when using the clinical diagnostic approach, thereby limiting the emergence and dissemination of drug-resistant strains and minimizing antibiotic-related toxicity.

Table 5.4 Various methods for microbiologic diagnosis and their yield

Methods	Quantitative culture	Sensitivity	Specificity
Endotracheal aspirate	$\geq 10^5$ CFU/mL	76 ± 9%	75 ± 28%
Bronchoscopy BAL PSB	$\geq 10^4$ CFU/mL $\geq 10^3$ CFU/mL	73 ± 18% 66 ± 19%	82 ± 19% 90 ± 15%
Blind mini BAL	$\geq 10^4$ CFU/mL	63–100%	66–96%

Step 1: Start therapy using broad-spectrum antibiotics

Step 2: Stop therapy if the diagnosis of infection becomes unlikely

Step 3: Use narrower spectrum antibiotics once the etiologic agent is identified

Step 4: Use pharmacokinetic-pharmacodynamic data to optimize treatment

Step 5: Switch to monotherapy on days 3 to 5

Step 6: Shorten the duration of therapy

Fig. 5.2 Stepwise strategy for antimicrobial therapy for VAP

The non-bronchoscopic techniques include mini-BAL and blind protected specimen brush. The advantage of these techniques is that they can be performed by individuals not qualified to do bronchoscopy. Mini-BAL involves insertion of one thin catheter through a large catheter, so that outer catheter works as a sheath for the inner catheter and preventing contamination from proximal airways (Table 5.4).

5.7 Treatment of VAP

The treatment of VAP is challenging and involves knowledge of likely causative organisms and spectrum of various antibiotics. It involves the usage of an appropriate antibiotic in optimal doses for adequate period. Antibiotic therapy in VAP is a two-stage process. First one involves initiation of broad-spectrum antibiotics for early treatment and second, narrowing the antibiotic use after cultures to prevent overuse and resistance. Empirical choice depends upon knowledge of likely organisms and local antibiotic susceptibility patterns. The aim is to obtain culture and sensitivity reports and then shift to monotherapy by day 3 whenever possible and reduce the duration of therapy to 7–8 days. A stepwise strategy for the same is shown in Fig. 5.2.

5.8 Initial Therapy

Failure to initiate prompt appropriate therapy has been linked with increased mortality in patients with VAP. Due to the emergence of multiresistant organisms such as P. aeruginosa, Klebsiella pneumoniae and Acinetobacter, and the increasing role of gram positive bacteria, such as MRSA, empirical treatment with broad-spectrum

Table 5.5 Empirical antibiotic regimen for treatment of VAP

Not at high risk of mortality and no risk factors	Not at high risk of mortality but with factors increasing the likelihood of gram negative bacteria	High risk of mortality or receipt of intravenous antibiotics during the prior 90 days
One of the following: Piperacillin-tazobactam 4.5 g IV q6h OR Cefepime 2 g IV q8h Levofloxacin 750 mg IV daily	Piperacillin-tazobactam 4.5 g IV q6h OR Cefepime or ceftazidime 2 g IV q8h OR Levofloxacin 750 mg IV daily Ciprofloxacin 400 mg IV q8h OR Imipenem 1 g IV q8h Meropenem 1 g IV q6h	Piperacillin-tazobactam 4.5 g IV q6h OR Cefepime or ceftazidime 2 g IV q8h OR Levofloxacin 750 mg IV daily Ciprofloxacin 400 mg IV q8h OR Imipenem 1 g IV q8h Meropenem 1 g IV q6h AND Amikacin 25 (30) mg/kg IV daily OR Gentamicin 5–7 mg/kg IV daily OR Tobramycin 5–7 mg/kg IV daily
	Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness) OR Linezolid 600 mg IV q12h	Vancomycin 15 mg/kg IV q8–12h with goal to target 15–20 mg/mL trough level (consider a loading dose of 25–30 mg/kg × 1 for severe illness) OR Linezolid 600 mg IV q12h

antibiotics is justified in most patients with a clinical diagnosis of VAP. The choice of agents should take into account the antibiotics that the patients have received within the prior 2 weeks, striving not to use the same antimicrobial classes.

The choice of empirical antibiotic therapy is shown in Table 5.5. Risk factors of multidrug-resistant VAP are prior intravenous use within 90 days, septic shock at VAP onset, acute respiratory distress syndrome preceding VAP, five or more days of hospitalization prior to VAP onset, and acute renal replacement therapy prior to VAP onset.

De-escalation of antibiotic therapy based on culture reports should be done. Successful treatment of patients with VAP requires serial clinical and microbiologic assessment. In responding patient the antibiotics should be given for 7–8 days. Long duration (14–21 days) of therapy is required in the following conditions:

- Multilobar consolidation
- Malnutrition
- Cavitation
- Gram −ve necrotizing pneumonia
- Isolation of MDR Pseudomonas, and Acinetobacter species

5.9 Prevention of VAP

Establishing well-designed ICU practices can lead to significant reduction in incidence of VAP. Prevention of VAP should be a priority goal of every ICU as it is associated with poor patient outcome. The whole staff should be educated about infection control policy and the procedure for the same. It should be monitored that all staff members are following the policy. Adequate resources should be provided for prevention of VAP. Regular surveillance data should be collected and should be communicated to staff to motivate for further improvement.

5.10 Handwashing

Routine handwash with soap and water and regular use of alcohol based hand rubs remain the most important strategy to reduce the risk of infection transmission. Hand wash should be used when hands are visibly soiled, before eating, after using the restroom and when exposed to C. difficile. Hand rub should be used before and after each contact with patient and patient's surroundings.

5.11 Semi-Recumbent Positioning

Supine positioning is associated with increased risk of reflux and aspiration. When it is feasible and patient can tolerate it, placing the patient in semirecumbent position (i.e. 30–45° elevation of head end) is a low cost measure for VAP prevention.

5.12 Selection of Endotracheal Tube

The use of orotracheal intubation is preferred over nasotracheal intubation. There are antibiotic coated and silver coated ET available. Silver coated tubes are associated with reduced risk of VAP but are not popular. The use of appropriate cuff pressure between 20 and 25 cm H_2O is associated with reduced chances of aspiration and it should be regularly monitored. Higher cuff pressures are associated with increased risk of mucosal injury, bleeding and tracheal stenosis. Even with this pressure there is formation of microchannels around the cuff causing aspiration. So the role of endotracheal tubes with subglottic suction port becomes important. Continuous or intermittent aspiration of subglottic secretions is now a recommended strategy for VAP prevention.

5.13 Ventilator Circuit Management

Reducing ventilator circuit changes is cost-effective and it reduces the incidence of VAP. Ventilator tubings should not be changed regularly unless they are non-functional or if they are visibly soiled with secretions or blood.

Use of certain humidifiers may be associated with increased bacterial transmission. Heat and moisture exchangers (HME) can filter bacteria and are more effective in reducing VAP than heated wire circuits and heated humidifiers. Use of in-line nebulizers is also associated with increased infection and they should be disinfected, rinsed with sterile water and air-dried.

5.14 Pharmacologic Interventions

5.14.1 Decontamination

Oropharyngeal decontamination with chlorhexidine has been shown to reduce the incidence of VAP. Selective digestive decontamination with oral antibiotics has not been recommended due to its ineffectiveness in prevention of VAP. It has been seen that skin decontamination with chlorhexidine, at ICU admission and regularly after that, leads to reduced VAP especially reduced incidence of MRSA VAP.

5.14.2 Stress Ulcer Prophylaxis

Most ICU patients receive stress ulcer prophylaxis in the form of gastroprotective agents like sucralfate or H_2 blockers or proton pump inhibitors. PPI increases gastric pH leading to increased gastric colonization, thus increasing chances of VAP but they have much higher benefit for stress ulcer prevention.

Suggested Readings

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Kalil AC, Metersky ML, Klompas M, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–e111.

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Blood Stream Infections

6

Bikash Ranjan Ray and Srikant Behera

6.1 Introduction

Intravascular catheters are required for patients of in-hospital and outpatient settings for various purposes, including fluid and medication administration; hemodynamic monitoring; renal replacement therapy; and nutritional support. Bloodstream infection (BSI) may occur as a complication of intravascular catheters in many hospitalized patients, most frequently in intensive care unit (ICU) settings. BSI is one of the most devastating conditions in ICU associated with high morbidity, prolonged length of hospital stay, high costs of treatment and, often may lead to mortality.

6.2 Definition

Bloodstream infections (BSI) may be defined as infectious diseases characterized by the presence of viable microorganisms (i.e., bacteria, fungus) in the bloodstream which elicits an inflammatory response, leads to alteration of clinical, laboratory, and hemodynamic parameters, and can be demonstrated by the recovery of a microbial pathogen in blood culture due to infection, not by virtue of specimen contamination (Viscoli 2016). BSI may be primary or secondary. BSI is primary when the central line which the patient has for ≥48 h is the only probable source of infection. Similarly BSI is secondary when there is an underlying cause for the BSI, i.e. respiratory infection /genitourinary infections or there is any other obvious source of infection in the body. BSI may also be classified as hospital-related BSI which occurred after a patient has completed ≥48 h of stay in the hospital and community acquired BSI (Bharadwaj et al. 2014).

Central line-associated bloodstream infection (CLABSI) as defined by the National Healthcare Safety Network (NHSN) is a laboratory-confirmed BSI in a

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patient who had a central line within the 48 h period before the development of the BSI, or the BSI within 48 h of removal of a central venous catheter and which cannot be attributed to an infection unrelated to the catheter and that is not related to an infection at another site. There is no minimum period of time that the central line must be in place in order for the BSI to be considered central line-associated, but there must have been one within 48 h of onset of infection. The confirmation of CLABSI requires both a positive blood culture and a collaborative clinical and microbiological review of the patient. It is used for the purpose of clinical setting and surveillance of health care-associated infection (Horan et al. 2008).

Catheter-related bloodstream infection (CRBSI) refers to BSI attributed to an intravascular catheter by quantitative culture of the catheter tip or by differences in growth between catheter and peripheral venipuncture blood culture specimens. This definition is primarily used in research.

Central venous catheter is an intravascular access device or catheter whose tip resides or terminates at or close to the heart or in one of the great vessels. It may be inserted centrally or peripherally. Central venous catheter and central line are used interchangeably.

6.3 Long-Term and Short-Term Central Venous Catheter

A long-term central venous catheter is a central venous catheter that is intended to remain in place for a prolonged or indefinite period of time and it is either tunnelled subcutaneously or fully implanted where as a short-term central venous catheter is intended for temporary use and it is neither tunnelled subcutaneously nor fully implanted.

Central line day is defined as one patient with one or more indwelling central venous catheters, residing in a health care facility at one point in time during a 24-h period.

6.4 Epidemiology

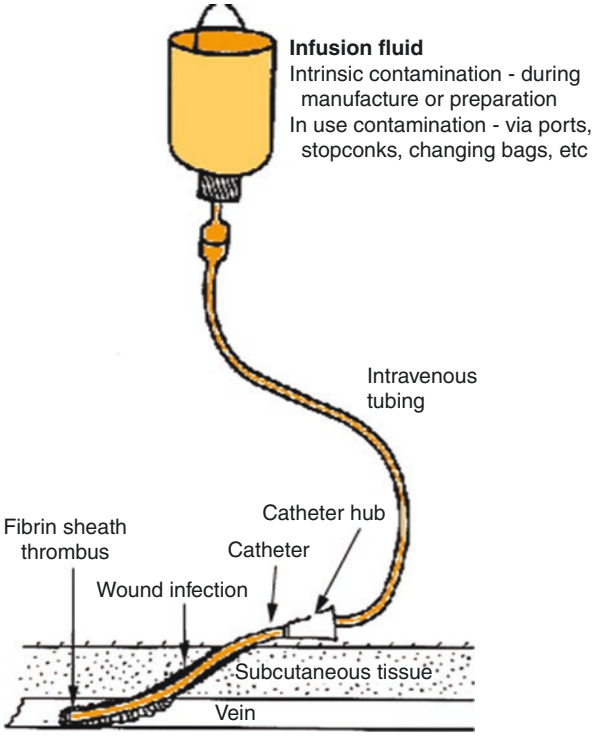
The rates of BSI differ markedly worldwide. CRBSIs are an important cause of morbidity and mortality globally. Although ICU patients are generally exposed to more invasive medical devices and are more severely ill than other hospitalized patients, CRBSIs also common in hospital wards outside the ICU. CVC is the commonest cause for CRBSI. Based on the United State's National Nosocomial Infections Surveillance (NNIS) data from January 1992 through June 2004 showed that the median rate of CRBSI in ICUs ranged from 1.8 to 5.2 per 1000 catheter days. Whereas another survey in 2010 showed mean incidence of CRBSI up to 1.76 per 1000 catheter days. Though, it suggests a decreasing trend of CRBSI, possibly as a result of widespread prevention efforts, still there is high burden of CRBSI

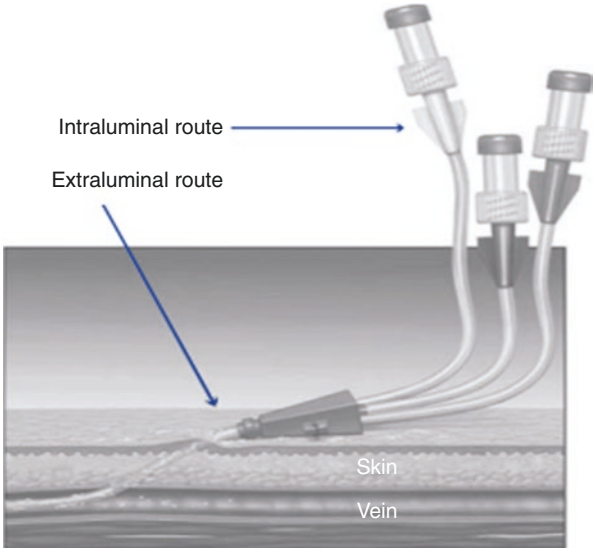
globally. The global incidence of CRBSI is 2.4–12.5 per 1000 catheter days. The incidence of CRBSI is even higher in Indian ICUs and it is as high as 16.1 per 1000 catheter days.

6.5 Pathogenesis

Several factors have been proposed in the pathogenesis of CRBSI. These factors are often interrelated. The catheter can be involved in 4 different pathogenic pathways in the development of CRBSI. BSI associated with CVCs mostly originates from four sources:

1. From the skin—skin colonization with migration of microorganisms along the intracutaneous tract (wound infection or infection of fibrin sheath),
2. Intraluminal or hub contamination,
3. Seeding from a BSI—hematogenous seeding from remote focus elsewhere,
4. Contamination of the infusate—the delivery of contaminated infusate is a rare cause of BSI.





Sources of intravenous catheter-related infection

Mechanisms

- contamination during insertion,
- contamination of insertion site (post-insertion),
- contamination of infused substance,
- subsequent contamination due to breaking of sterile connection (multi-flow, 3-way taps),
- subsequent contamination from systemic infection.

Bacterial migration

- migration of microbes from catheter–skin interface extraluminally to the catheter–vessel interface (most common situation),
- migration from hub intra-lumenally.

Insertion site

- subclavian generally preferred,
- higher rates of CLABSI with internal jugular access in tracheostomy patients,
- some studies suggest greater colonization and infection of central lines at the femoral site followed by the jugular,
- femoral access may have higher rates of CLABSI in patients with a high BMI.

6.6 Etiology

Aerobic gram-negative bacteria were the predominant organisms associated with BSIs till the end of 20th century. In the modern era, gram-positive aerobes and *Candida* species have increasingly recognized as BSI causing pathogens. Majority of catheter-related bloodstream infections are caused by coagulase-negative staphylococci, *S. aureus*, enterococci, and candida species. The common organisms associated with BSIs (in decreasing frequencies) are: Coagulase-negative staphylococci (16.4%), Enterococci (15.2%), *Candida* species (13.3%), *S. aureus* (13.2%), *Klebsiella* species (8.4%), *Escherichia coli* (5.4%), *Enterobacter* species (4.4%), and *Pseudomonas* species (4%). CVC-related infection due to anaerobic bacteria is exceedingly rare (Weiner et al. 2016).

Certain pathogens are associated with specific host, treatment, and catheter characteristics. *S. aureus* infections are disproportionately represented in infections of hemodialysis catheters. Gram-negative bacilli have been associated with infections of patients with cancer, and they are typically the pathogens recovered in instances of infusate contaminations. Gram-negative bacilli and yeast have been affiliated with catheters placed in femoral veins, while candida has been associated with infections of lines used for administration of parenteral nutrition. When a cluster of cases of BSI are recognized involving the same organism, then it should be promptly investigated for the possibility of contaminated infusate.

6.7 Risk Factors

Risk factors for CRBSI may be classified as patient-, catheter-, and operator-related factors.

Patient-Related Factors Increasing severity of illness, granulocytopenia, compromised integrity of the skin, presence of distant infection, etc.

Catheter-Related Factors Catheter type, number of lumens (risk increasing with increasing lumen number), duration in situ, antimicrobial coating (antiseptic or antimicrobial coating of catheters can reduce risk of CRBSI), etc. For nontunneled catheters, risk of bloodstream infection varies by anatomic site of insertion such that risk is greatest for groin insertion, intermediate for neck insertion, and lowest for chest or upper extremity insertion.

Operator Factors Breaks in aseptic technique during placement and maintenance, frequent catheter access, etc. increase the risk.

6.8 Clinical Features

The clinical manifestations of BSI include fever, chill, inflammation, or purulence at the insertion site, hemodynamic instability, altered mental status, catheter dysfunction (due to intraluminal clot), and clinical features of SIRS or sepsis that often starts abruptly after catheter infusion. Fever is the most common and most sensitive clinical manifestation of BSI but it has poor specificity. Similarly inflammation or purulence at the insertion site though has greater specificity but poor sensitivity. Complications related to a BSI such as suppurative thrombophlebitis, endocarditis, osteomyelitis, and metastatic infection may also be found. In patients of under 1 year age group having fever (>38 °C core) hypothermia (less than 36 °C core), apnea, or bradycardia may be the clinical features of BSI.

6.9 Diagnosis

CRBSI should be suspected in a patient with an intravascular catheter in situ or removed within previous 48 h who develops the clinical or laboratory criteria of the systemic inflammatory response syndrome (SIRS) or a new onset sepsis or worsening of sepsis/septic shock without an obvious, nonvascular site of infection. The diagnosis of BSI is based on the positivity of blood cultures. Two positive blood cultures are preferred for common skin contaminants, to avoid ascribing the etiology to a pathogen that was actually not present in the bloodstream, with obvious therapeutic mistakes and possible dramatic consequences. So, at least 2 blood cultures should be taken, one blood culture should be obtained by peripheral venipuncture and at least one blood culture should be obtained from a lumen of the catheter. The skin as well as the hub of the catheter to be cleansed with alcohol, tincture of iodine or alcohol chlorhexidene, and allowed to dry before specimen collection, in order to reduce the incidence of contamination of blood culture. If the catheter is removed for suspected infection, quantitative culture of the distal 5 cm tip should be performed. When the tip of a catheter is sent for culture, 2 blood cultures may be taken by peripheral venipuncture. If a patient is having multiple central catheters, blood culture should be drawn from each catheter as well as one blood culture obtained by peripheral venipuncture (Mermel et al. 2009a).

Time to detection of growth or incubation time is a reliable surrogate measure of the microbial load in the blood obtained for culture. A diagnosis of CRBSI is made if any of the following 3 criteria is fulfilled:

1. Same organism recovered from peripheral venipuncture blood culture and from quantitative (>15 colony-forming units) culture of the catheter tip.
2. Same organism recovered from a peripheral venipuncture blood and a catheter lumen blood culture, with growth detected in catheter lumen blood 2 h sooner.

3. Same organism recovered from quantitative culture of both percutaneous and catheter lumen blood, with at least threefold greater colony count in the catheter lumen blood.

For multilumen catheters, blood cultures may be taken from each lumen of the catheter suspected of infection, and 1 blood culture from peripheral venipuncture for enhanced detection of CRBSI (Guembe et al. 2010).

6.10 Assessment for CRBSI

Assessment for CRBSI should be done if there is evidence of SIRS in a patient with a central line, or one who had a central line within 48 h.

1. Assess exit site of CVC.
2. Assess for other sources of infection.
3. Assess for diagnostic criteria.

6.11 Treatment

Systemic antibiotic therapy is usually not required in circumstances like positive catheter tip culture in the absence of clinical signs of infection, and positive blood cultures obtained through a catheter with negative cultures from peripheral venipuncture sample, in the absence of clinical features suggestive of infection.

Catheter management: The first step in treatment of systemic intravenous catheter-related infection requires determination regarding catheter management (e.g., removal, salvage, or exchange). Catheter removal is warranted in circumstances like severe sepsis, hemodynamic instability, endocarditis or evidence of metastatic infection, erythema or exudate due to suppurative thrombophlebitis, persistent bacteremia after 72 h of antimicrobial therapy to which the organism is susceptible, etc. The nature of the pathogen is also important while taking decisions regarding catheter removal. Short-term catheters should be removed in the setting of CRBSI due to *Staphylococcus aureus*, enterococci, gram-negative bacilli, fungi, and mycobacteria. Similarly long-term catheters should be removed in CRBSI due to *S. aureus*, *Pseudomonas aeruginosa*, fungi, or mycobacteria. Catheter removal is not necessary for hemodynamically stable patients with unexplained fever in the absence of documented bloodstream infection and without endovascular prosthetic material such as a prosthetic valve, pacemaker, etc. Catheter salvage may be attempted in the setting of uncomplicated CRBSI involving long-term catheters due to pathogens other than *S. aureus*, *P. aeruginosa*, fungi, or mycobacteria. In circumstances where catheter removal is necessary but risk of complications during catheter reinsertion is high, guide wire exchange of the catheter may be appropriate (Mermel et al. 2009b; Bouza et al. 2007).

6.12 Antibiotic Therapy

Empiric antibiotic therapy must be instituted when CRBSI is suspected after taking appropriate cultures and subsequently, therapy should be tailored according to microbiology results as needed. The initial choice of antibiotics depends on the clinical circumstances, including the severity of illness, the risk factors for infection, and the likely pathogens associated with the specific intravascular device.

Empiric therapy of CRBSI in health care settings should consist of vancomycin. Daptomycin to be used in place of vancomycin in facilities where there is increased prevalence of methicillin-resistant *S. aureus* with reduced vancomycin susceptibility (minimum inhibitory concentration >2 mcg/mL). Empiric coverage for gram-negative organisms is required in the setting of increased severity of illness or femoral catheterization. Similarly, antibiotics active against *Pseudomonas aeruginosa* should be started in the setting of neutropenia, severe illness, or known colonization. Antimicrobials active against candida, preferably an echinocandin, to be started empirically in the setting of femoral catheterization, total parenteral nutrition, prolonged administration of broad-spectrum antibiotics, hematologic malignancy, or solid organ, or hematopoietic stem cell transplantation (Mermel et al. 2009c). Following initiation of empiric antibiotic therapy, therapy should be tailored to culture and susceptibility results as needed once data are available. If blood cultures fail to yield growth, the need for further empiric antibiotic therapy should be reassessed.

6.13 Duration of Therapy

For uncomplicated bloodstream infection, i.e., in the absence of supportive thrombosis, endocarditis, or metastatic infection and in the absence of factors that increase the risk of hematogenous spread of infection like intravascular hardware, immunosuppression, etc. systemic therapeutic, intravenous antibiotic treatment is recommended for: 5–7 days for coagulase-negative staphylococci; 7–14 days for enterococci and Gram-negative bacilli; 14 days in the absence of evidence fungal retinitis for *Candida* species; and 14 days in the absence of evidence of endocarditis clinically and by transesophageal echocardiography for *S. aureus*.

6.14 Prevention

A prospective cohort study by Pronovost et al. showed a significant decrease in CRBSI when the following elements were carried out as a bundle of care (Pronovost et al. 2006):

1. Hand washing.
2. Full barrier precautions during insertion of CVLs (mask, hair cap, sterile gloves, gown, and full-sized sterile drape).

3. Clean skin with chlorhexidine (2%) and allow drying.
4. Avoid femoral site if possible.
5. Removing unnecessary catheters early.
6. Education.
7. CVC cart.
8. Checklist for infection control.
9. Providers stopped if practices were not adhered to (not in emergencies).
10. Removal of catheters discussed daily at rounds.
11. Catheter-related bloodstream infection rates/month communicated to teams.

Evidence-based recommendations for prevention of catheter-related bloodstream infections are summarized below.

6.15 Recommendations for the Prevention of Intravascular Catheter-Related Infections (O'Grady et al. 2011)

1. Limit insertion to trained personnel.
2. Avoid use of the femoral vein.
3. Use subclavian vein in lieu of the internal jugular or femoral vein depending upon risk of injury during insertion.
4. Use a central venous catheter with the minimum number of lumens required for patient care.
5. Complete hand hygiene prior to insertion and assessment or dressing change of catheter exit site.
6. Prepare clean skin of insertion site with >0.5% chlorhexidine plus alcohol.
7. Do not administer systemic antimicrobial prophylaxis.
8. Use a chlorhexidene/silver sulfadiazine or a minocycline−/rifampin-impregnated central venous catheters when the local rate of central line-associated bloodstream infection is not declining despite.
   (a) Education of optimal insertion and maintenance practices.
   (b) Use of maximum sterile barrier precautions during insertion.
   (c) Use of >0.5% chlorhexidene plus alcohol for preparation of skin before insertion.
9. Use maximum sterile barrier precautions, including cap, mask, sterile gown, sterile gloves, and a sterile full-body drape for insertion and during guide wire exchange. New sterile gloves before inserting new catheter during exchange over guide wire.
10. Place semipermeable transparent or gauze dressing over insertion site.
    (a) Gauze favored when exit site is bloody or moist.
    (b) Restrict application of antimicrobial ointment to exit sites of hemodialysis catheters and only then when approved for use by catheter manufacturer.
    (c) Assess exit site daily
        • Visually for transparent dressings.
        • By palpation for gauze dressings (remove for visual inspection if tender).

(d) Exchange exit site dressing whenever damp, loosened, or soiled
- Replace gauze dressings every 2 days.
- Replace semipermeable transparent dressings every 7 days.

11. When adherence to aseptic technique was compromised during insertion, replace the catheter as soon as possible.
12. Do not routinely replace central venous catheters to prevent infection.
13. Remove any intravascular catheter as soon as it is no longer required for patient care.

Adherence to recommended practices is associated with significant declines in the rates of these infections. Optimization of multidisciplinary care to reduce risk of CRBSI at the level of units within hospitals and collaborations between facilities to enhance adoption of all processes of care intended to reduce risk of CRBSI has been associated with significant declines in the frequency of these infections (Shah et al. 2013).

6.16 Future Thought

Many infections can be detected after 24–48 h, but it may take up to 5-day incubations to capture the slow-growing bacteria and fungi associated with BSI, and the antibiotic susceptibility testing requires an additional 6–24 h. Therefore several days of empirical treatment with broad-spectrum antibiotics to be given before culture directed therapy. The empirical use of antibiotics results in a 15–30% rate of inappropriate treatment, which is associated with a two to fivefold increase in the mortality risk of septic patients and a contributing factors in the recent increases in antibiotic-resistant organisms. In addition, the diagnostic yield of conventional microbiologic methods is low, especially in patients treated prior to sampling and in cases of uncultivable or fastidious organisms. Also, many culture-negative, molecular-positive detections are likely to be due to culture insensitivity rather than a lack of specificity or clinical relevance of molecular methods. Blood culture is positive in only 50% of cases where BSI is strongly suspected from a clinical point of view. Fast and sensitive molecular techniques for the detection of sepsis-related pathogens are urgently needed, especially from primary blood sample.

6.17 Conclusion

BSIs are an important cause of morbidity and mortality. Nosocomial BSIs are common in ICU and most of them are due to CRBSI. CRBSI are costly complications of hospital care, more commonly in the ICU settings. Presence of intravascular catheters, duration of catheterization, catheter material, insertion conditions, and site care are the risk of CRBSI. The skin microbiome (coagulase-negative staphylococci and *Staphylococcus aureus*) is the most important source of intravascular catheter infection. Gram-negative pathogens predominate in patients with

hematologic and nonhematologic malignancies. Infections related to the administration of contaminated intravenous fluids are rare but should be suspected when bacteremia occurs in an otherwise low-risk patient or when there is a cluster of bloodstream infections with unusual organisms. Infections with multidrug-resistant organisms are associated with high rates of treatment failure and death. Risk of these infections can be reduced by optimizing catheter selection, insertion and maintenance, and by removing catheters when they are no longer needed. Diagnosis of CRBSI can be established with certainty by culture of appropriately collected blood sample and catheter tips. When CRBSIs occur in the ICU, physicians must be prepared to recognize and treat them. Evidence-based guidelines should be followed for antibiotic treatment and catheter management when these infections occur. The rate of CLABSI is a marker of quality of care.

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Urosepsis

7

Devanshu Bansal, Prabhjot Singh, and Brusabhanu Nayak

7.1 Definition

Sepsis is defined as life-threatening organ dysfunction due to dysregulated host response to infection. Sepsis is differentiated from infection by the presence of aberrant or dysregulated host response and presence of organ dysfunction. A variety of sources in body may lead to sepsis syndrome, including respiratory system (most common), gastrointestinal tract, and genitourinary tract. Urosepsis is defined as life-threatening organ dysfunction due to dysregulated host response to infection originating from the urinary tract and/or male genital organs (e.g., prostate) (Singer et al. 2016) and may be a cause for substantial patient morbidity and economic burden on the healthcare system. This chapter describes the epidemiology, pathophysiology and management approach to a patient with urosepsis.

7.2 Epidemiology

The global incidence of urosepsis ranges from 9 to 31% across different parts of the world and across different reports in the literature (Levy et al. 2012). Severe sepsis is generally caused by respiratory or abdominal causes, with urosepsis accounting for 5% of the cases in community acquired setting. However, in cases of nosocomial sepsis, this proportion may be as high as 40% (Kalra 2009). Depending on the organ source, mortality rates associated with sepsis may vary. Although, nearly 25% cases of sepsis originate from the genitourinary tract (Thornton et al. 2018), urosepsis generally has a lower mortality compared to other sources, with reported mortality rates of 20–40% for patients with severe urosepsis. Prompt management of

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ureosepsis leads to successful outcome in majority of cases (Dreger et al. 2015; Hotchkiss and Karl 2003). Sepsis is generally seen more commonly in men compared to women; however, urosepsis is more common in women (Kalra 2009).

7.3 Risk Factors

The most common precursor for urosepsis is complicated urinary tract infection, defined as urinary tract infection occurring in a patient with some underlying anatomical or functional abnormality which predisposes to severe infection. This may include anatomical changes in the urinary tract leading to urinary stasis or altered host immunity like diabetes or azotemia. This leads to suboptimal efficacy of antimicrobial therapy and higher rates of antimicrobial resistance (Kalra 2009). Risk factors for urosepsis may also be divided into systemic and local factors, as follows

1. Systemic factors.
   (a) Elderly patients.
   (b) Diabetes mellitus.
   (c) Immunosuppression.
   (d) Transplant recipients.
   (e) Patients on cancer chemotherapy.
   (f) Steroid intake.
   (g) Azotemia.
   (h) Neutropenia.
2. Local factors.
   (a) Urinary tract obstruction (78%).
      (i) Congenital (e.g., phimosis, urethral stricture, ureterocele, ureteric stricture).
      (ii) Acquired (e.g., prostatic hypertrophy, urinary tract calculi, urinary tract malignancies, pregnancy, radiation therapy).
   (b) Impaired voiding.
      (i) Vesicoureteral reflux, cystocele, neurogenic bladder.
   (c) Endourological procedures.
      (i) Indwelling urethral catheter, ureteric stent, percutaneous nephrostomy.
      (ii) Endourological procedures.

7.4 Pathogenesis and Pathophysiology

The offending organisms commonly causing urosepsis include gram negative bacteria, gram positive (15%) bacteria, and fungi (in nosocomial setting and immunocompromised hosts), with gram negative enterobacteria being the most common. *Escherichia coli* is the most common among gram negative bacteria causing urosepsis and accounts for almost 52% of the cases. Other offending bacteria include

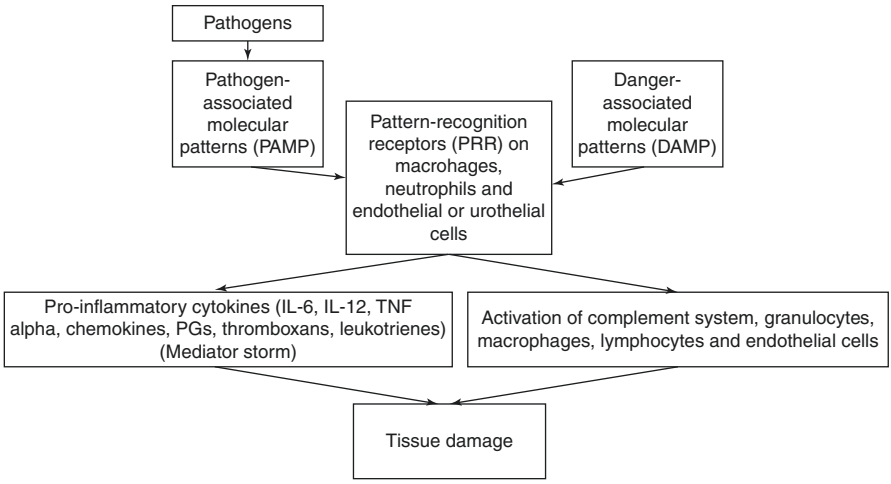

Fig. 7.1 Pathophysiology of urosepsis

1. *Proteus* spp. (15%).
2. *Enterobacter* spp. (15%).
3. *Klebsiella* spp. (15%).
4. *Pseudomonas aeruginosa* (5%) (Dreger et al. 2015; Vikrant et al. 2018).

Urinary tract infections most commonly begin by colonization of urethral or vaginal meatus with pathogenic bacteria and fecal flora which reach the urinary bladder via the urethra. Such organisms may further ascend to the kidneys and lead to pyelonephritis. Hematogenous seeding of kidneys or infection by direct extension from a contiguous source is a much less common route of infection. Once the infection gets established, the host response is initiated and that defines the severity of sepsis. A flow diagram for the pathophysiology of urosepsis is given in Fig. 7.1.

7.5 Diagnosis

The diagnosis of urosepsis requires presence of symptoms and signs suggestive of urinary tract infection, along with features of systemic inflammatory response syndrome (SIRS). Clinical categorization of patients can then be done so as to estimate the severity of urosepsis and guide patient management.

1. Symptoms and signs—Urosepsis may have a varied presentation. Therefore, it is important to look for clinical features pointing towards a urologic source of infection. These may include flank pain, urinary frequency, dysuria, or occasionally urinary retention and scrotal or prostatic pain. Fever, chills with hypotension may be absent in almost two-third of cases. Patient should be examined thoroughly including a general physical examination including pulse rate and volume,

Table 7.1 Features of SIRS

Body temperature	≥ 38 °C or ≤36 °C
Tachycardia	≥ 90 beats/min
Tachypnea	≥ 20 breaths/min
Respiratory alkalosis $PaCO_2$	≤ 32 mmHg
Leucocytes	≥ 12,000 cells/uL or ≤ 4000 cells/uL or band forms >10%

abdominal examination to look for flank tenderness, digital rectal examination to rule out prostatitis or prostatic abscess, and a scrotal examination for possible epididymorchitis. Presence of indwelling urinary catheter or ureteric stents/nephrostomy tubes should also be considered as possible sources of infection. Apart from symptoms localizing the infection to the genitourinary tract, features of systemic inflammatory response syndrome should be looked out for (Table 7.1).

2. Clinical categorization.
   (a) The Second Consensus Conference for Sepsis defined sepsis as the presence of evidence of bacteremia or clinical suspicion of sepsis accompanied by two or more criteria of SIRS.
   (b) The Third International Consensus Definition for Sepsis and Septic Shock recommends use of SOFA score for clinical characterization of patients with sepsis. In the absence of pre-existing organ dysfunction, the baseline SOFA score is considered as zero. Patients who are found to have a SOFA score of 2 or more have a higher overall mortality with a risk ~10% (Singer et al. 2016).
   (c) Screening of patients likely to have sepsis may also be done with the use of quick SOFA (qSOFA) score. This incorporates altered mentation, systolic blood pressure of 100 mmHg or less, respiratory rate of 22/min or greater and is useful to identify adult patients with suspected infection likely to have poor outcomes. A positive qSOFA should prompt further patient evaluation for possible infection (Singer et al. 2016).
   (d) The task force defines septic shock as a subset of sepsis in which mortality risk is significantly increased due to abnormalities in circulatory and cellular metabolism. Such patients can be identified with the presence of sepsis with persistent hypotension requiring vasopressor support (to maintain mean arterial pressure ≥ 65 mmHg) and serum lactate level > 2 mmol/L in spite of adequate volume resuscitation. In-hospital mortality in such cases exceeds 40% (Singer et al. 2016).
3. Microbiological diagnosis—Samples from urine, two sets of blood cultures, and aspirated fluids should be sent for bacterial examination and culture (Urological infections. EAU guidelines 2019). For infections not responding to standard antimicrobial treatment and those in immunocompromised hosts, testing for atypical organisms including fungal stains and cultures should be sent. Blood and urine for microbiological testing and culture should be taken before initiating empirical antibiotics to avoid false negative results. However, accuracy of

such cultures may not be optimal even in the setting of urosepsis, with only 30% of blood cultures yielding true positive results. Similarly, in obstructive pyelonephritis, the sensitivity and specificity of urine cultures may be as low as 30.2% and 73%, respectively (Dreger et al. 2015).

4. Biochemical markers—Several new markers for diagnosis of sepsis are available and may be used to guide treatment in limited clinical settings. However, majority of upcoming markers need further evaluation to be incorporated in treatment guidelines. These include
   (a) Serum procalcitonin—Serum procalcitonin rises in presence of severe generalized infections (bacterial, parasitic, and fungal) and has moderate to no elevation in severe viral infections or inflammatory reactions (Brunkhorst et al. 2000). Levels below 0.5 ng/mL make a diagnosis of severe sepsis or septic shock highly unlikely, whereas levels above 2 ng/mL imply the converse (Dreger et al. 2015). Use of serum procalcitonin has shown to reduce the total duration of antibiotics in patients with sepsis without increasing mortality (Brunkhorst et al. 2000; Schuetz et al. 2009).
   (b) Serum lactate—Serum lactate is a marker of organ dysfunction and raised levels are associated with higher mortality in sepsis (Mikkelsen et al. 2009).
   (c) Mid-regional pro-adrenomedulline.
   (d) Serum cytokine IL-6 levels.
5. Imaging—Ultrasonography remains the first line investigation for evaluation of urosepsis and acts as an extension of the physical examination. It readily identifies the presence of hydronephrosis, suggests the presence of pyonephrosis, renal, prostatic, and testicular abscesses and can be used for monitoring the size of infected collections and for guided diagnostic and therapeutic drainage of infected material. Up to 93% of common causes of urosepsis including hydronephrosis or prostatic abscess may be identified by an ultrasound. Ultrasound does not carry with itself any harms of ionizing radiation and is safe for use in pregnancy. However, it remains operator dependent as of now. Plain abdominal radiography has limited value in cases of urosepsis except for diagnosing and monitoring for change of position for renal calculi and identification of renal calcifications. In the presence of equivocal ultrasound findings, computed tomography is the optimal imaging modality, and may be useful to detect previously undetected collections or abscesses in cases of persistent sepsis.

7.6 Management

Management of urosepsis should be prompt and often requires multi-modal inputs from intensive care and infectious disease specialists. Organisms causing urosepsis are usually more resistant to antibiotics compared to strains causing uncomplicated urinary tract infection (Kalra 2009). Adequate supportive care, appropriate and timely antibiotic therapy and drainage of urinary obstruction and large infected collections and abscesses form the crux of management.

7.7 Prevention of Nosocomial Urosepsis (Urological infections. EAU guidelines 2019)

1. Isolation of patients infected with multi-resistant organisms to avoid cross infection.
2. Limited and appropriate prophylactic use of antibiotics before any urologic intervention.
3. Early patient discharge.
4. Early removal and indwelling urethral catheters and ureteral stents as permitted.
5. Use of closed catheter drainage system.
6. Minimally invasive methods to release urinary tract obstruction till patient stabilization.
7. Use of universal precautions including proper hand-hygiene.

7.8 Treatment

1. Antimicrobial therapy.
   (a) Initiation of empirical antibiotics till a microbiological diagnosis is available is an integral part of treatment with initiation of empirical antibiotics within the first hour being associated with a significantly better survival (80%) compared to delayed antibiotic treatment. In a study by Kumar A et al., a delay of every hour in starting empirical antibiotics was associated with a 7.6% decline in patient survival (Kumar et al. 2006). Samples should always be obtained for blood, urine, and drainage fluid culture before starting empirical antibiotics. Commonly chosen empirical antibiotics for urosepsis include a third-generation cephalosporin, piperacillin-beta lactamase inhibitor combination or a fluoroquinolone. The final choice for empirical antibiotics is guided by local susceptibility patterns and the choice of antimicrobial therapy should be modified according to the culture results, preferably within 48–72 hours. Doses of antibiotics may need to be modified in the presence of renal/hepatic dysfunction commonly associated with sepsis. Treatment is usually given for 14 days and patients who fail to respond clinically within 48 to 72 hours should be investigated for hidden source of sepsis.
2. Source control.
   (a) It is of paramount importance to drain and decompress the infected component of the urinary tract. Merely starting antibiotics without source control will not lead to improvement in patient condition. This may involve placing a simple per-urethral catheter in cases of benign enlargement of prostate with obstructive uropathy with sepsis or in some cases may require placement of ureteric double J stents or percutaneous nephrostomy. Patients with epididymorchitis/prostatitis are better managed with placement of a suprapubic catheter for urinary drainage so as to not obstruct the natural orifices of ejaculatory or prostatic ducts, respectively. Abscess in any location deemed by the urologist too large to be managed only by antibiotics should be expeditiously drained with a pigtail catheter and fluid sent for microbiological analysis.

3. Supportive measures.
   (a) All patients with sepsis should be aggressively resuscitated. Patient should be started on oxygen by facemask and monitored for development of hypoxemia, hypercapnia, altered sensorium, or respiratory muscle fatigue. Patients may need to be intubated if clinically indicated. Ventilated patients should be on stress ulcer and pressure sore prophylaxis and should be adequately sedated.
   (b) Initial isotonic crystalloid bolus should be given with the goal of administering at least 30 mL/kg body weight in the first hour. However, caution must be exercised in cases of obstructive uropathy with deranged renal function as these patients may in fact be volume overloaded and may not tolerate an additional fluid challenge. Such patients require emergent dialysis followed by prompt source control. Patients should be monitored for possible post-obstructive diuresis and serum electrolytes and intake output should be closely monitored. The goal should be to maintain a pulmonary capillary wedge pressure of 12–16 mmHg or central venous pressure of 8–12 cm of water. Oliguria should be prevented, with a minimum urine output aimed at least 0.5 ml/kg/h.
   (c) Patients unable to maintain a mean arterial pressure > 65 mmHg and a cardiac index of more than or equal to 4 L/min/m^2 despite adequate fluid resuscitation should be started on vasopressors. Hydration status should be monitored with central venous pressure measurement and monitoring of IVC fullness. Noradrenaline is the vasopressor of choice in cases of septic shock.
   (d) Patients with urosepsis with underlying chronic kidney disease are commonly anemic and adequate transfusion of packed red blood cells is indicated to maintain a hemoglobin level above at least 7 gm/dl.
   (e) Blood glucose should be regularly monitored and hypoglycemia should be avoided. Prophylaxis for deep vein thrombosis should be administered. Patients developing disseminated intravascular coagulation may need support with blood products, including fresh frozen plasma and donor platelets.
4. Conclusion—Urosepsis is a severe form of urinary tract infection associated with significant morbidity and mortality in untreated cases. Prompt diagnosis and management with multidisciplinary collaboration with nephrologists, microbiologists, radiologists, and critical care specialists is essential for a positive outcome.

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Infections of the Central Nervous System (CNS) in the ICU

8

Deepti Vibha and Divyani Garg

Key Points

- CNS infections necessitate admission and close monitoring in the ICU as they may lead to complications of raised intracranial pressure, status epilepticus, coma, and high mortality.
- They are caused by a wide array of microorganisms leading to distinct clinical syndromes that include bacterial and fungal meningitis, viral encephalitis, brain abscess, and post-operative CNS infections.
- Clinical assessment should be thorough to look for systemic clues to the etiology, e.g., typical rash in meningococcal meningitis, vesicular rash in herpes, presence of ear discharge, or sinusitis in acute pyogenic meningitis as well as brain abscess. These are vital pointers towards diagnosis.
- Rapid constitution of guided empirical antimicrobial therapy is the mainstay of management and should not be deferred for diagnostic tests as this may increase morbidity and mortality.

8.1 Introduction

Infections of the central nervous system (CNS) encompass a range of potentially life-threatening infections. They often require acute management and careful monitoring in an intensive care setup. The most common causes of ICU admission due to CNS infections include acute bacterial meningitis, acute viral encephalitis, tuberculous meningitis, fungal meningitis, neurocysticercosis, abscess, and myelitis. Problems necessitating ICU admission related to these infections include raised intracranial pressure, status epilepticus, neurological deficits, and coma necessitating ventilatory support. Acute CNS infections have mortality rates that range from

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20 to 25% in acute bacterial meningitis (Mandell et al. 2009), 70% in herpes simplex encephalitis without treatment (30% with treatment) (Daroff et al. 2016), and up to 30–40% in Japanese encephalitis (Solomon et al. 2000).

In this chapter, we attempt to provide an overview of the epidemiology, presenting features, evaluation, and management principles of this disease spectrum.

8.2 Epidemiology in India

In a study from 1997 from India, neurological infections accounted for 2.3–10.5% of admission to ICUs. CNS problems had a high mortality (64%), with meningitis and encephalitis having mortality of 68% (Udwadia et al. 1997). In other study from southern India, these accounted for 8.7–51% of all admissions to ICU (Meena et al. 2001). Among patients who are admitted to ICU with coma, neurological infections accounted for 20–57% of all cases (Desai and Vijayaraghavan 1991). In a study from northern India, 70% of the patients requiring neurological ICU care were of tubercular meningitis or viral encephalitis (Misra et al. 2014).

8.3 Etiology and Pathophysiology

CNS infections may be bacterial, viral, fungal, mycobacterial, or parasitic (Table 8.1) (Tunkel et al. 2004). Focal infections within the cerebral parenchyma initially lead to cerebritis, which may then form an abscess. Involvement of cerebral veins leads to septic venous thrombophlebitis. Host immunity plays an important role in determining the extent of infection and, hence, the clinical manifestations of neurological infections.

Involvement of the CNS may be through direct involvement or via the hematogenous route. Direct inoculation occurs via traumatic breach of the natural defenses of skin, soft tissue, and bone. Hematogenous spread may occur via arterial or venous dissemination, which breaches the blood–brain and blood–CSF barriers. Once the organism gains access to the subarachnoid space, there is proliferation due to the immune-deprived nature of the subarachnoid space.

8.4 Approach to the Patient

Patients with CNS infections usually present with fever, headache, and altered mental status. This triad may be seen in patients with encephalopathy due to sepsis as well. Hence, other clinical clues must be sought to establish a clinical diagnosis of meningitis, encephalitis, or cerebral abscess. Patients with meningitis may complain of neck stiffness in addition, may demonstrate signs of meningeal irritation in the form of neck stiffness, Kernig's and Brudzinski's signs. Chronic meningitis such as tuberculous or fungal may lead to basal exudates and entrapment of the cranial nerves. Patients with acute viral encephalitis like herpes simplex may have

Table 8.1 List of etiological agents causing CNS infections (Tunkel et al. 2004)

Organism	Common agents
Bacterial	*Streptococcus pneumoniae* *Neisseria meningitidis* *Staphylococcus aureus* Group B streptococcus *Listeria monocytogenes* *Klebsiella pneumoniae* *Haemophilus influenzae* *Escherichia coli*
Viral	Herpes simplex virus (1 and 2) Human herpesvirus-6 Cytomegalovirus Varicella zoster virus Enteroviruses Human immunodeficiency virus West Nile virus
Fungal	*Cryptococcus neoformans* *Blastomyces dermatitidis* *Histoplasma capsulatum* *Coccidioides immitis* Candida Aspergillus
Mycobacterial	Tuberculosis
Protozoan	Acanthamoeba Naegleria Toxoplasma Plasmodium species

additionally seizures. Focal neurological signs may be found in patients with abscesses, and in these patients, signs to suggest a focus such as chronic suppurative otitis media, and sinusitis should be sought.

8.5 Clinical Features and Evaluation

8.5.1 Bacterial Meningitis

This is an important cause of acute CNS infection throughout the world. The age of occurrence has shifted from 30 to 41.9 years due to the increased use of the *Haemophilus influenzae* and *Streptococcus pneumoniae* vaccines (Tunkel et al. 2004). Despite a decrease in the incidence of the same by almost 30%, the mortality of acute bacterial meningitis remains unchanged at 15% (Thigpen et al. 2011). The epidemiology of the causative organisms also continues to be the same, with *Streptococcus pneumoniae* being the leading cause, followed by *H. influenzae* and *Neisseria meningitides* (Tunkel et al. 2004). However, age group is the most important determinant of the causative organism. In children below 2 years of age, group B streptococci form the major chunk, whereas above 2 years of age, *S. pneumoniae*

Table 8.2 Etiology of acute bacterial meningitis and empirical intravenous antibiotic therapy (Tunkel et al. 2004)

Underlying condition	Etiology	Empirical antibiotic therapy
Age < 2 months	Group B streptococci, *E. coli, H. influenzae, S. pneumoniae, L. monocytogenes*	Ampicillin + cefotaxime or ampicillin + aminoglycoside
2–23 months	*S. pneumoniae, N. meningitidis*, group B streptococci, *H. influenzae*	Vancomycin + third-generation cephalosporin
2–50 years	*S. pneumoniae, N. meningitidis*	Vancomycin + third-generation cephalosporin
>50 years	*S. pneumoniae, N. meningitidis, L. monocytogenes, H. influenzae*	Vancomycin + ampicillin + third-generation cephalosporin
Basilar skull fracture	*S. pneumoniae, H. influenzae*, group A streptococci	Vancomycin + third-generation cephalosporin
Penetrating trauma	*S. aureus*, coagulase-negative staphylococci, gram-negative bacilli	Vancomycin + cefepime, vancomycin + ceftazidime, vancomycin + meropenem
Post-neurosurgical	Pseudomonas species, *S. aureus*, coagulase-negative staph	Vancomycin + cefepime, vancomycin + ceftazidime, vancomycin + meropenem

S. pneumonia: *Streptococcus pneumoniae*
S. aureus: *Staphylococcus aureus*
E. coli: *Escherichia coli*
H. influenza: *Hemophilus influenzae*
N. meningitides: *Neisseria meningitideis*
L. monocytogenes: *Listeria monocytogenes*

and *N. meningitides* acquire greater importance. In individuals above 65 years of age as well as alcoholics, *Listeria monocytogenes* becomes an increasingly important consideration and is associated with higher mortality (Thigpen et al. 2011; Weisfelt et al. 2010) (Table 8.2).

Patients may present with the classical triad of fever, headache, and neck stiffness, all three components of which are seen in <50% of cases (van de Beek et al. 2004). One third may have focal neurological deficits (van de Beek et al. 2004).

A patient suspected to have acute bacterial meningitis should have urgent neuroimaging, especially if the patient has focal neurological deficits, clinical signs of raised intracranial pressure such as papilledema, moderate to severe impairment of consciousness, or immunocompromised state. This is done prior to the lumbar puncture to assess the risk of herniation due to raised intracranial pressure. Close differentials for acute bacterial meningitis include subdural empyema, subdural hemorrhage, and brain abscess which are easily differentiated on neuroimaging.

Lumbar puncture reveals raised CSF opening pressure, with CSF pleocytosis with white cell count ranging from 100 to 10,000 cells/mm^3, with neutrophilic predominance (van de Beek et al. 2004). In 5–10% of cases, there may be lymphocytic predominance or the absence of pleocytosis which is associated with a poor prognosis (Bonadio 1992). Protein levels are elevated (above 45 mg/dL) and sugar level is decreased. Gram stain and culture is the gold standard for the diagnosis of acute bacterial meningitis. Gram stain has sensitivity between 60 and 90% and

specificity of 88% prior to the initiation of antibiotic therapy (van de Beek et al. 2004; van de Beek et al. 2006). Although the sensitivity of CSF culture is reduced to 55% following administration of antibiotics within 4 h, there is no significant impact on sensitivity of Gram stain (Nigrovic et al. 2008). Culture helps to establish the diagnosis, identify the causative organism, and also enable in vitro antibiotic sensitivity analysis. Other tests such as bacterial antigen testing in CSF as well as PCR assays may be useful if Gram stain and culture are negative (van de Beek et al. 2006; Saravolatz et al. 2003). CSF lactate concentration of >4.0 mmol/L is found to favor bacterial meningitis and may be especially useful in post-neurosurgical meningitis (Thigpen et al. 2011). Blood culture must also be obtained in these patients.

8.5.1.1 Treatment of Bacterial Meningitis

Empirical intravenous antibiotic therapy must be initiated emergently even prior to neuroimaging or lumbar puncture, particularly if a delay is anticipated. Therapy is emergent as mortality rates triple if there is a delay in therapy by 6 h (Miner et al. 2001).

Role of Steroids in Acute Bacterial Meningitis

Adjunctive corticosteroids are initiated in these patients for the management of cerebral inflammation and raised intracranial pressure. Steroids have been shown to reduce complications in infants and children with meningitis due to *H. influenzae* and in adults due to *S. pneumoniae* (McIntyre et al. 1997; de Gans and van de Beek 2002). A randomized trial determined that the addition of steroids reduced the morbidity from 25 to 15% and mortality from 15 to 7% (de Gans and van de Beek 2002). There was also a trend towards reduced rates of deaths and hearing loss with dexamethasone therapy in meningococcal meningitis (Heckenberg et al. 2012). The IDSA 2004 guidelines suggested that adjunctive corticosteroids should be considered in all patients with suspected or diagnosed bacterial meningitis and were indicated in all adult patients with suspected or proven pneumococcal meningitis (Thigpen et al. 2011). Studies from the developing world, however, do not demonstrate clear benefit with adjunctive steroids in children and adults with meningitis (Nguyen et al. 2007; Scarborough et al. 2007). These issues were addressed in a large meta-analysis which questioned the mortality benefit of corticosteroids in the developing world in patients with meningitis (Heckenberg et al. 2012; Brouwer et al. 2015). As per IDSA guidelines, based on available data, steroids must be administered in all adults with suspected or proven pneumococcal meningitis in the developed world. In the developing world, this is left to the discretion of the treating physician.

8.5.2 Viral Encephalitis

Encephalitis implies inflammation of the brain parenchyma and is most commonly due to infection with viral organism. Differentials include encephalopathy, which is a diffuse cerebral dysfunction not associated with inflammation, and a

post-infectious immune-mediated process such as acute disseminated encephalomyelitis (ADEM). A very close mimic is autoimmune encephalitis, especially associated with antibodies to N-methyl D-aspartate (NMDA) receptor. Patients with viral encephalitis present with complaints of fever, headache, altered sensorium, and seizures. This may be preceded by a prodrome of myalgia, rash, coryza, and joint pains. Changes in the level of consciousness in association with fever ensue. Seizures may be focal or generalized. There may be other focal deficits associated such as hemiparesis, aphasia, and ataxia (Chaudhuri and Kennedy 2002). Specific clinical clues on general examination such as parotitis in the case of mumps, vesicular rash in the case of varicella zoster virus (VZV), and herpetic rash in the case of herpes simplex virus (HSV) infection may point to particular organisms and must be carefully sought. Features of parkinsonism such as bradykinesia, rigidity, tremor may be seen in association with Flavivirus infections such as West Nile virus, Japanese B encephalitis, St. Louis encephalitis virus as they involve the basal ganglia and the thalamus. Cerebellar ataxia occurs in Epstein Barr virus (EBV), VZV, mumps, and Flaviviruses. Anterior horn cell involvement is seen in Flaviviruses, poliomyelitis, and enterovirus 71. Brainstem involvement is seen in Flaviviruses, enterovirus 71, and HSV. Cranial nerve palsies are uncommon in viral encephalitides but may occur as part of brainstem involvement. HSV infection is the most common and eminently treatable of the viral encephalitides. Clinical picture is of acute altered mentation, olfactory hallucinations, memory impairment, and confusion, in the background of fever and headache. The virus has a predilection for involvement of the mesial temporal and limbic pathways, leading to the above clinical manifestations. Early initiation of therapy with intravenous acyclovir improves prognosis which may otherwise be associated with high mortality, as well as morbidity, in the form of cognitive and behavioral sequelae, as well as post-infectious epilepsy. CT or MRI imaging of the brain characteristically reveals asymmetrical involvement of the mesial temporal and orbitofrontal lobes with T2/FLAIR hyperintensity (Tyler 2004) (Fig. 8.1). MRI is more sensitive than CT (Domingues et al. 1998). Similar findings occur in HHV-6 encephalitis. Subependymal enhancement is seen in CMV encephalitis. Multifocal hemorrhagic foci occur in varicella encephalitis (Gilden et al. 2007). The CSF shows lymphocytic pleocytosis with elevated protein and normal sugar levels. Neutrophilic predominance is seen in some Flavivirus infections (particularly WNV) (Tyler et al. 2006). Sugar levels may be low in mumps, CMV, and Eastern Equine encephalitis. CSF PCR for some neurotropic viruses has high sensitivity and specificity. HSV PCR has a sensitivity of 98% and specificity of 94% (Lakeman and Whitley 1995). The sensitivity declines with duration of antiviral therapy (Lakeman and Whitley 1995). The sensitivity of CSF PCR for Flaviviruses is lower (57–70%). Electroencephalography (EEG) may also help in the diagnosis. Most patients with viral encephalitis demonstrate generalized slowing (Solomon et al. 2007). However, in HSV encephalitis, 75–80% may demonstrate focal abnormalities in the form of frontotemporal slowing, temporal sharp waves or spikes, as well as periodic lateralized discharges (Whitley et al. 1982; Domingues et al. 1997).

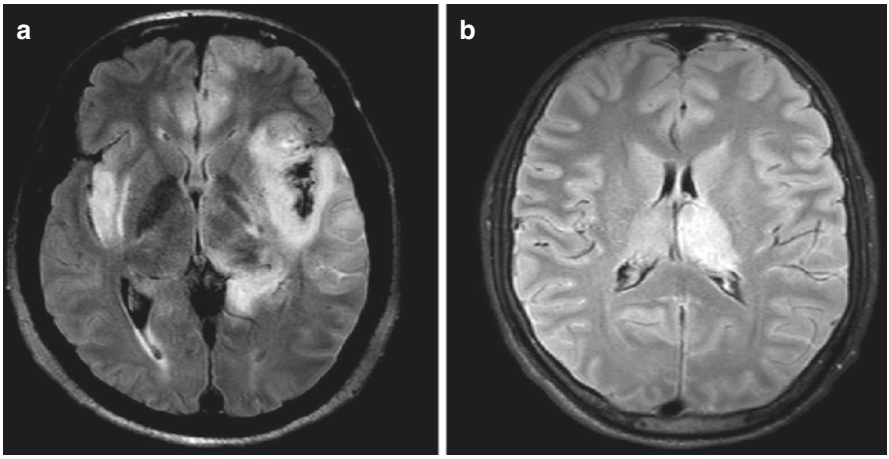

Fig. 8.1 (**a**) HSV encephalitis—FLAIR axial brain MRI showing asymmetrical temporal, insular, and bifrontal hyperintensities. (**b**) Japanese B encephalitis—FLAIR axial brain MRI showing asymmetrical (left > right) bilateral thalamic hyperintensities

8.5.2.1 Treatment of Viral Encephalitis

In all cases of suspected herpes virus encephalitis, treatment with intravenous acyclovir should be initiated urgently at 30 mg/kg in three divided doses. For children, the dose is 60 mg/kg. Studies indicate that prognosis worsens in these patients with delay of therapy, including death and disability. These patients may be obtunded, requiring intubation and mechanical ventilation for airway protection. Complications include autonomic dysfunction which manifests as cardiovascular instability, leading to hypotension and cardiac arrhythmias, and should be monitored using continuous blood pressure and electrographic monitoring. There is some evidence of steroids for viral encephalitis (Kamei et al. 2005). Raised intracerebral pressure (ICP) must be managed with other measures including hyperventilation or hypertonic solutions. Another complication of viral encephalitis is the development of seizures which should be immediately aborted with intravenous benzodiazepines including intravenous lorazepam or midazolam, followed by loading and maintenance dose antiepileptic drugs.

Duration of therapy with antiviral agents should be continued for 14–21 days and 21 days in immunocompromised individuals.

8.5.3 Cerebral Abscess

The most common source of a bacterial cerebral abscess is from oto-rhinological infections, followed by traumatic inoculation and pulmonary sources. The clinical features depend on the location of the abscess, and comprise fever, headache, altered sensorium, and focal neurological deficits. The latter may present as sensorimotor

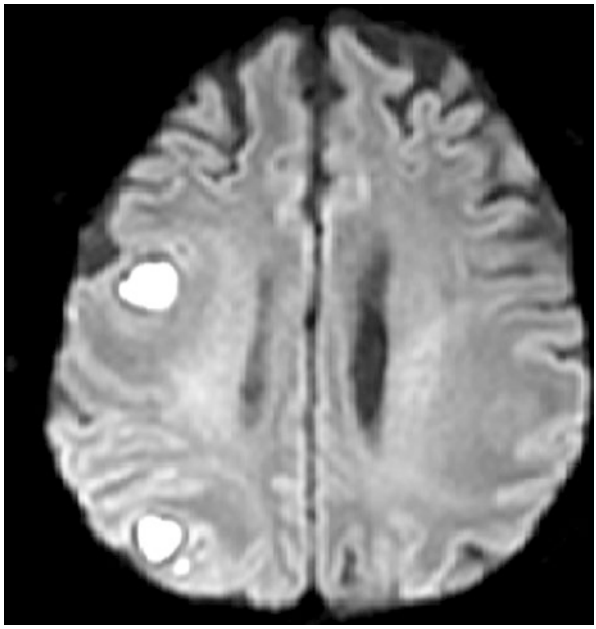

Fig. 8.2 Brain abscess—Diffusion weighted axial MRI brain demonstrating two well-defined, rounded lesions with diffusion restriction

weakness, focal seizures, and ataxia (Carpenter et al. 2007). Clinical clues for the source of infection must be looked for in the form of chronic suppurative otitis media, mastoiditis, or paranasal sinus infection. The primary diagnostic modality is neuroimaging in the form of CT or MRI. Lumbar puncture is not advisable due to raised intracranial pressure and the subsequent risk of cerebral herniation. Contrast-enhanced CT scan shows the presence of a well-defined hypodense area surrounded by a thin rim of contrast enhancing wall. MRI brain is preferred for the diagnosis. On T1-weighted images, the abscess has a thin wall isointense to the brain parenchyma that demonstrates contrast enhancement. The abscess appears hypointense on T2-weighted images and demonstrates diffusion restriction (Fig. 8.2) (Lu et al. 2006). The etiological organism is determined by the predisposing factor. Streptococci are most commonly cultured from bacterial brain abscesses and, in up to 60% of the cases, may be associated with mixed etiology, including Gram-negative bacterial and anaerobes. Other organisms include Bacteroides spp., Proteus, and Pseudomonas. Staphylococcus aureus forms an important cause in patients with bacterial endocarditis (Prasad et al. 2006). Management is determined by the size of the abscess. Abscesses larger than 2.5 cm require drainage, either via stereotactic guidance or excision. Contiguous foci in the form of sinusitis or mastoiditis should be looked for and managed surgically simultaneously to prevent further infection (Alvis Miranda et al. 2013). Empirical antibiotic therapy should be initiated as soon as the diagnosis is made. Duration of therapy requires at least 4 weeks of intravenous therapy which may be further extended to as long as 8 weeks based on clinical and radiological response. Empirical therapy of brain abscess is elucidated in Table 8.3 (Prasad et al. 2006).

Table 8.3 Empirical antibiotic therapy for brain abscess based on contiguous focus of infection (Prasad et al. 2006)

Contiguous infection	Site of abscess	Causative organisms	Antimicrobial therapy
Otogenic infection	Temporal lobe, cerebellum	Streptococcus spp., Bacteroides, Pseudomonas, Enterobacteriaceae	Ceftazidime or Cefepime + Metronidazole
Paranasal sinusitis	Frontal lobes	Streptococcus, Peptostreptococcus, Fusobacterium, Bacteroides	Third-generation cephalosporin + metronidazole
Hematogenous spread	Parietal, temporal, or frontal	Source of primary infection:	
		(1) Endocarditis: *Streptococcus viridans, Staphylococcus aureus*, Enterococcus	Vancomycin, third-generation cephalosporin, metronidazole
		(2) Intra-abdominal infection: Gram-negative bacilli, enterococcus, anaerobes	Vancomycin, third-generation cephalosporin, metronidazole or vancomycin, and meropenem
		(3) Pulmonary infection: Strep species, anaerobes, fusobacterium	Third-generation cephalosporin and metronidazole
		(4) Urinary tract infection: Gram-negative bacilli	Third-generation cephalosporin and metronidazole
Penetrating trauma		*Staph. aureus*, coagulase-negative staph., Clostridium species, aerobic gram-negative bacilli, Bacteroides species	Vancomycin, third-generation cephalosporin, and metronidazole
Post-operative		*Staph. aureus*, CONS, Pseudomonas, anaerobes, enterobacteriaceae	Vancomycin, cefepime and metronidazole or vancomycin, and meropenem

CONS coagulase-negative staphylococci

8.5.4 CNS Tuberculosis

CNS TB includes three main categories: tuberculous meningitis (TBM), tuberculomas, and spinal arachnoiditis (Bourgi et al. 2017). The rupture of a subependymal tubercle with progression and rupture into the subarachnoid space leads to infection in the meningeal space (Rich and McCordock 1933). Meningitis may also occur from reactivation bacillemia that may occur as a result of immune deficiency (ageing, malnutrition, alcoholism, HIV infection, diabetes, etc.). Tuberculous meningitis leads to three predominant pathological reactions responsible for clinical manifestations (Dastur et al. 1995). These include arachnoiditis which leads to a

proliferative fibrous encasement at the base of the brain, including blood vessels and cranial nerves. Vasculitis leads to thrombosis leading to a variety of stroke syndromes. Communicating hydrocephalus may also occur from extension of the inflammatory exudates to the basal cistern. Tuberculomas are caseous foci within the brain parenchyma that develop from tubercles spreading to the brain by hematogenous dissemination. Spinal arachnoiditis may occur at single or multiple levels leading to progressive encasement of the cord.

Patients with TBM may be classified into various stages of severity as follows (Commitee 1948):

- Stage I: Lucid with no focal neurological signs.
- Stage II: Lethargic, confused, and mild focal deficits such as cranial nerve palsies.
- Stage III: Coma, stupor, and multiple cranial nerve palsies.

Diagnosis of CNS TB can be challenging and relies on both CSF examination and radiological signs.

CSF shows low sugar with elevated protein with a mononuclear pleocytosis. CSF protein ranges from 100 to 500 mg/dL but may exhibit very high levels associated with xanthochromia and a poor prognosis. The usual CSF cell count is usually between 100 and 500 cells/μL. Early in the course of the disease, the CSF may exhibit polymorphonuclear pleocytosis. CSF adenosine deaminase level cannot be used to distinguish TB from bacterial meningitis. A meta-analysis of ten studies estimated the sensitivity and specificity of CSF ADA to be 79 and 91%, respectively, for the diagnosis of TB meningitis (Xu et al. 2010). CSF acid-fast bacilli smears may be positive in up to 37% of cases, although the yield increases further with large volumes of CSF and repeated studies (Kennedy and Fallon 1979). However, empirical therapy need not be delayed for this result. Nucleic acid amplification tests should be administered on the CSF. WHO in 2017 issued recommendations favoring the use of Xpert MTB/RIF Ultra assay as an initial test for the diagnosis of tuberculous meningitis (WHO 2017). In a systematic review and meta-analysis, the sensitivity and specificity for the Xpert MTB/RIF assay compared with culture in CSF were 81 and 98%, respectively (Denkinger et al. 2014). These nucleic acid amplification tests can be used to confirm the diagnosis of CNS TB but not rule out the disease.

Findings on CT and MRI may include basilar meningitis, tuberculomas (Fig. 8.3), cerebral edema, infarction, and hydrocephalus.

Treatment is with antitubercular drugs. These consist of an initial intensive phase (four drugs administered for 2 months) followed by a prolonged continuation phase. Glucocorticoids are indicated because they reduce death and disability from tuberculous meningitis by about 25% (Prasad et al. 2016). Patients with hydrocephalus may require CSF diversion procedures to manage raised intracranial pressure if they have altered sensorium. In the case of isoniazid resistance, another anti-TB agent such as fluoroquinolones and injectable aminoglycosides may be added to the standard regimen. The duration of therapy should be extended to 18–24 months.

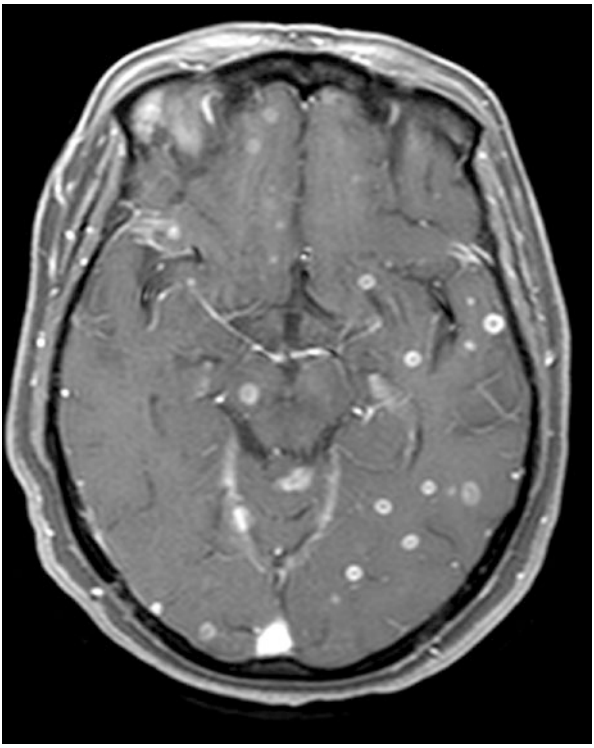

Fig. 8.3 Tuberculous meningitis with tuberculomas-T1-contrast-enhanced axial MRI brain demonstrating multiple ring-enhancing tuberculomas and cisternal enhancement suggestive of meningitis

8.5.5 CNS Toxoplasmosis

Toxoplasmosis is caused by the intracellular protozoan parasite, Toxoplasma gondii. Primary infection in immunocompetent hosts is usually asymptomatic. After the initial infection, latent infection can persist and may get reactivated in immunocompromised individuals such as those with HIV/AIDS. The parasite completes its reproductive cycle in the feline animal where it infects the epithelial cells of the gut. Infectious oocysts are excreted in the feces of the feline which are subsequently ingested by human beings (Tenter et al. 2000). The organism then invades the intestinal epithelial cells and gains access to nucleated cells throughout the body in which it lies dormant till reactivated. In patients with HIV, this occurs when the CD4 count drops below 100 cells/mm^3 (Porter and Sande 1992). The most common site of reactivation is the CNS. Extracerebral toxoplasmosis is much less common. Patients with toxoplasma encephalitis present typically with headache, fever, and confusion (Porter and Sande 1992). Focal neurological deficits and seizures may also occur. Diagnosis is based on classical neuroimaging abnormality and serology. Serology is based on the presence of positive anti-toxoplasma IgG antibodies. These start increasing 1–2 weeks following infection and reach a peak within 6–8 weeks. CT or MRI may also reveal typical findings. These are hypodense lesions that exhibit ring-like contrast enhancement and perilesional edema. A highly suggestive

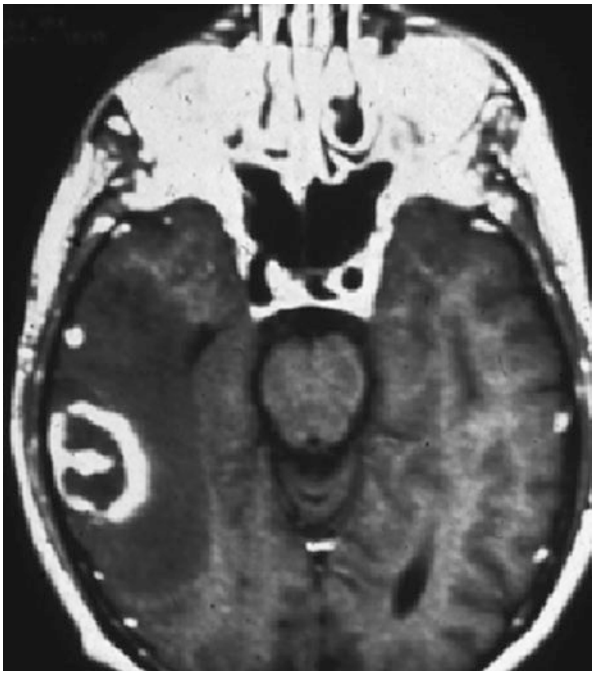

Fig. 8.4 Toxoplasmosis. T1-contrast-enhanced axial MRI brain showing "eccentric dot" sign defined by an eccentric nodule along ring-like wall enhancement

though uncommon radiological sign is the "eccentric target" sign in which an eccentric nodule along the wall of the enhancing ring is seen (Fig. 8.4). On T1-weighted MRI, these may be iso- to hypointense and iso- to hyperintense on T2-weighted MRI.

Treatment of toxoplasmosis is listed in Table 8.4 (Porter and Sande 1992).

8.5.6 Cerebral Malaria

This is the most severe complication caused by Plasmodium falciparum malaria. The parasite is transmitted by Anopheles spp. mosquito, and this complication may develop after 2–7 days following malarial fever (Brabin et al. 2000). This is clinically defined as the presence of unarousable coma in a patient with malaria. Hence, the diagnosis of P. falciparum needs to be confirmed and other causes of encephalopathy need to be ruled out. Accompanying complications include anemia, metabolic acidosis, and hypoglycemia (Taylor et al. 1990). Patients with cerebral malaria have high mortality rates and survivors may be left with significant sequelae with behavioral and cognitive deficits (Idro et al. 2005). The pathogenesis is believed to be sequestration of infected red blood cells in the cerebral microcirculation leading to brain capillary occlusion and endothelial swelling (Dorovini-Zis et al. 2011). This leads to obstruction of blood flow with hypoperfusion and decreased delivery of nutrients, causing clinical features such as encephalopathy and seizures. The prognosis worsens with the coexistent renal dysfunction, liver dysfunction, and

Table 8.4 Treatment and prophylaxis regimes of CNS toxoplasmosis (Porter and Sande 1992)

First choice	Sulfadiazine oral 1000 mg (<60 kg) q6h+ Pyrimethamine oral 200 mg loading dose, then 50 mg (<60 kg) to 75 mg (≥60 kg) PO qd+ Folinic acid (leucovorin) oral, IV, IM, 10–20 mg qd (≤50 mg qd) Clindamycin oral or IV, 600 mg q6h (IV ≤ 1200 mg q6h) Pyrimethamine oral 200 mg loading dose then 50 mg (<60 kg) to 75 (≥60 kg) mg PO qd + Folinic acid (leucovorin) oral, IV, IM 10–20 mg QD (≤50 mg qd)	Duration: At least 4–6 weeks after the resolution of all signs and symptoms
Alternative	Pyrimethamine + Folinic acid + one of the following: – Atovaquone oral 1500 mg q12h – Clarithromycin oral 500 mg q12h – Azithromycin oral 900–1200 mg qd – Dapsone oral 100 mg qd Co-trimoxazole oral or IV 5 mg/kg (trimethoprim component) q12h	
Maintenance regimens		
First choice	Same as treatment regimen but halves doses Discontinue if >200 CD4 cells/mic.L for >3 months (asymptomatic with normal MRI or without contrast enhancement on MRI)	
Alternative	Co-trimoxazole 2 tab 960 mg qd	
Primary prophylaxis regimens		
Standard	Co-trimoxazole 1–2 tab or 480–960 mg qd	
Alternative	Dapsone 50 mg qd Dapsone 50 mg qd + Pyrimethamine 50 mg/week + Folinic acid 25 mg/week	

qd = once daily, q6h = every 6 hourly, q12h = every 12 hourly

metabolic acidosis. Up to 50% of patients with cerebral malaria may experience seizures. The overall mortality from adult cerebral malaria is around 20% (Newton et al. 2000). The mortality rises with the degree of extracerebral organ involvement. Complications of cerebral malaria include protracted seizures, prolonged coma, hypoglycemia, and severe malaria. This is a medical emergency demanding urgent treatment. The diagnosis is made by isolation of parasite in the peripheral smear. CSF is essentially normal and helps to exclude alternative diagnosis. Specific parenteral antimalarial treatment is the only intervention that unequivocally affects the prognosis of patients with cerebral malaria. Table 8.5 (Sethi et al. 2012) outlines the parenteral agents used for treatment.

8.5.7 Fungal Meningitis

This is among the most severe CNS infections. Its incidence has increased in association with human immunodeficiency virus (HIV). Other predisposing factors include corticosteroid use, hematopoietic stem cell transplantation, neutropenia, diabetes mellitus, lymphoma, chronic diseases including malignancy, hereditary immune defects, intravenous drug abuse as well as breakdown of the blood–brain

Table 8.5 Antimalarial treatment of cerebral malaria (Sethi et al. 2012)

Loading	Maintenance	
Cinchona alkaloid		
Quinine dihydrochloride		
Intravenous	7 mg/kg salt over 30 min (infusion pump) followed immediately by 10 mg/kg over 4 h 20 mg salt/kg over 4 h	10 mg/kg over 4 h repeated every 8–12 h Same as above
Intramuscular 20 mg salt/kg (dilute iv formulation to 60 mg/ml given by deep im injection divided between both anterior thighs)	10 mg salt/kg repeated every 8–12 h	
Quinine gluconate Intravenous	10 mg salt/kg infused over 1–2 h or 20 mg salt/kg infused over 4 h	0.02 mg salt/kg/min continuously for up to 72 h 10 mg salt/kg infused over 4 h every 8–12 h
Artemisinin derivatives		
Artesunate – Intravenous	3.2 mg/kg	1.6 mg/kg repeated 12–24 hourly
Artemether – Intramuscular	3.2 mg/kg	1.6 mg/kg repeated 12–24 hourly

barrier due to surgery or trauma. Cryptococcal meningitis and Aspergillosis, however, have been reported in patients without these traditional immunocompromised states. Small fungi such as cryptococcosis, coccidioidomycosis, blastomycosis, and histoplasmosis gain access to the cerebral microcirculation from where they spread to the CSF and the leptomeninges. They also reach the brain parenchyma along the Virchow-Robin spaces along the small penetrating vessels, as well as the large vessels in the subarachnoid space. This results not only in leptomeningeal but also parenchymal involvement (meningoencephalitis). Fungal meningitis usually leads to chronic meningitis, although it may cause a subacute presentation as well. Acute presentations of fungal meningitis are rare, except in ICU and immunocompromised patients. Patients may present with general features of meningitis including headache, fever, altered sensorium, neck stiffness, features of raised intracranial pressure including papilledema, and focal deficits including cranial nerve palsies. Fungal meningitis may be due to the relatively common cryptococcal meningitis or rarer causes such as dimorphic or filamentous (septate and non-septate) fungi. In a study from northern India, the most common fungal organisms were determined to be Cryptococcus (34%), Aspergillus (16%), and Mucormycosis (50%) (Sethi et al. 2012). Rhinocerebral involvement is common with the Zygomycetes (Mucor) whereas skull base involvement is more common with Aspergillus. Other CNS involvement includes meningitis, meningoencephalitis, granulomas, vasculitis leading to infarcts, subarachnoid and intracerebral hemorrhage due to mycotic aneurysms, as well as spinal involvement in the form of epidural abscess, myelitis, or granulomas. Cryptococcal meningitis is the most common form of fungal meningitis, particularly in immunocompromised patients, especially HIV patients.

Fungal meningitis may also lead to acute vascular events, which may be ischemic or hemorrhagic. Especially in Aspergillosis and Zygomycosis, involvement of the skull base and angioinvasion leads to thrombotic occlusion in the major cerebral vessels including the internal carotid artery and its branches, as well as the vertebrobasilar system leading to strokes.

Cryptococcal meningitis is caused by the fungus *Cryptococcus neoformans*. Patients present with headache along with meningismus as well as signs of hydrocephalus with impaired cognition, seizures, urinary incontinence, gait disturbances, and ataxia. The usual habitat is in bird droppings. CSF reveals lymphocytic pleocytosis with elevated protein and low sugar. CSF may show positivity for India Ink as well as cryptococcal antigen. Diagnostic gold standard is growth of the organism on culture.

8.5.7.1 Treatment of Fungal Meningitis

As compared to bacterial meningitis, fungal meningitis tends to be more indolent and required prolonged periods of therapy. Management usually consists of three phases: induction, consolidation, and maintenance.

The patient also requires treatment of the underlying immunological problem and surgical debridement where possible. Table 8.6 (CDC n.d.) summarizes chief features and treatment of some important forms of fungal meningitis.

Table 8.6 Treatment strategies for fungal meningitis—adapted from https://www.cdc.gov/meningitis/fungal.html (CDC n.d.)

Fungus	Treatment
Cryptococcosis	
• HIV patients	Induction: Amphotericin B + flucytosine for 2 weeks Consolidation: Oral fluconazole 400 mg/day for 8 weeks Maintenance: Oral fluconazole 200 mg/day for 1 year
• Organ transplant	Induction: Lipid-formulation amphotericin + flucytosine for 2 weeks Consolidation: Oral fluconazole 400–800 mg/day for 8 weeks Maintenance: Oral fluconazole 200–400 mg/day for 6–12 months
• Immunocompetent patients	Induction: Amphotericin B + flucytosine for 4 weeks Consolidation/maintenance: As for organ transplant
• Raised ICP	If ICP >25 cm H2O and symptomatic, remove CSF by lumbar puncture to closing pressure <20 cm or ≤50% of opening pressure. Recheck OP daily till stable for 2 days. Consider ventriculostomy or lumbar drain if requiring daily LP
Candidiasis	Induction: IV lipid-formulation amphotericin ± flucytosine for several weeks Consolidation/maintenance: Fluconazole 400–800 mg until CSF and radiologic abnormalities resolve
Mucormycosis	Aggressive surgical debridement Standard or lipid-formulation amphotericin Some prefer echinocandin or posaconazole
Aspergillosis	Primary therapy: Voriconazole Salvage therapies: Liposomal amphotericin, posaconazole Surgical resection if possible
Histoplasmosis	Induction: IV lipid-formulation amphotericin for 4–6 weeks Consolidation/maintenance: Itraconazole ≥12 months and resolution of CSF abnormalities including Histoplasma antigen

8.5.8 Post-Operative Central Nervous System Infections (PCNSI)

Post-surgical CNS infections are a serious complication in patients undergoing neurosurgical procedures and require immediate management. These include meningitis, epidural or subdural empyema, and abscesses (Marion 1991; Nathoo et al. 1999a, b). The reported rates of PCNSI range from <1% to >8% in various studies, with higher rates if prophylactic antibiotics are not administered (Raggueneau et al. 1983; Mollman and Haines 1986). In a study published from Bangalore, India, 415 of 18,092 patients who underwent neurosurgical procedures developed infection (Srinivas et al. 2011). The incidence of meningitis was 2.2%. The incidence was higher (7.7%) in patients who had a pre-existing infection like post-pyogenic meningitis or tuberculosis hydrocephalus. The most common organisms were non-lactose fermenting Gram-negative bacillus, *Pseudomonas*, and *Klebsiella*. The methicillin-resistant *Staphylococcus aureus* strains were isolated in 2.6% of the patients. The overall mortality was 5%. In a large prospective multicenter study of 2944 adults who underwent craniotomy (Korinek et al. 2006), the independent risk factors for infection were CSF leakage and a subsequent operation while the independent predictive risk factors were non-elective surgery, clean-contaminated and dirty wounds, operative time >4 h, and more recent neurosurgery. Usage of antibiotic prophylaxis was not a factor (Korinek et al. 2006). In the study by Patir et al. (1992), the risk factors for post-operative infection were altered sensorium, multiple operations, pre-existing infection, emergency surgery, duration of surgery for more than 4 h, urinary catheterization, cerebrospinal fluid leak, and ventilatory support.

8.6 Differential Diagnosis

8.6.1 Encephalopathy

Encephalopathy refers to diffuse cerebral dysfunction in the absence of infection of the central nervous system. The most common causes include toxins, metabolic factors, and sepsis. The common toxins include alcohol and illicit drugs. Metabolic factors include hypoglycemia, hyperglycemia, hypo- or hypernatremia, hypo- or hypercalcemia, renal dysfunction, and hepatic dysfunction. The presence of fever in combination with headache, peripheral blood leukocytosis, as well as the presence of CSF pleocytosis favors the meningitis or encephalitis over encephalopathy. Patients with meningitis, in addition, display clinical signs of meningeal irritation. Neuroimaging reveals patterns typical for encephalitis and EEG also may show focal findings.

8.6.2 Subarachnoid Hemorrhage

Patients with subarachnoid hemorrhage (SAH) present with acute thunderclap headache associated with impairment of sensorium. Similar to bacterial meningitis,

SAH produces neck stiffness. The differentiating features include severe headache at onset and the absence of fever, favoring SAH. In addition, plain CT of the brain reveals the presence of blood in the subarachnoid spaces. CSF will show the presence of red blood cells.

8.6.3 Non-infectious Meningitis

This may occur due to a variety of causes including drugs-induced, non-infectious inflammatory diseases like sarcoidosis, systemic lupus erythematosus (SLE), Wegener's granulomatosis, etc., as well as chemical meningitis. There will be clues on history to suggest the presence of predisposing conditions.

8.6.4 Acute Disseminated Encephalomyelitis (ADEM)

This is a usually monophasic post-infectious or post-vaccinal immune-mediated demyelinating process that is a differential for viral encephalitis. The incidence is 0.4–0.8 per 100,000 of the population (Xiong et al. 2014). Clinical presentation is with altered sensorium as well as features of spinal cord involvement 1–2 weeks following an infection or vaccination. MRI shows features of demyelination, with T2-weighted images showing subcortical hyperintense lesions with perilesional edema, along with involvement of the thalamus and the brainstem. There may be punctate, arc-like or ring-like enhancement (Marin and Callen 2013). Diffusion weighted imaging demonstrates peripheral restriction but unlike cerebral abscess, the core does not demonstrate diffusion restriction. CSF picture is similar to viral encephalitis, with lymphocytic pleocytosis, elevated protein, and normal sugar. Histopathology reveals the presence of perivenular inflammation and demyelination, unlike viral encephalitis where perivascular inflammation occurs. Treatment necessitates intravenous methylprednisolone, and intravenous immunoglobulin or cyclophosphamide in steroid-refractory cases.

8.6.5 Autoimmune Encephalitis

This may be a differential for herpes encephalitis. Autoimmune encephalitis is an antibody-mediated immune process predominantly affecting the limbic system, which may be paraneoplastic (antibodies targeting intracellular antigens with poor response to immunotherapy) and non-paraneoplastic (antibodies targeting extracellular antigen with better response to immunotherapy) (Dalmau and Graus 2018). Patients develop subacute memory impairment, personality changes, psychiatric issues, as well as seizures. Fever may also be present. The most common antibodies are anti-Hu (associated with small cell lung cancer), anti-NMDA NR1 (associated with ovarian teratomas), and anti-NMDA NR2 (seen in SLE patients). Other antibodies are detailed in the table below along with the associated condition. MRI

shows the presence of T2/FLAIR hyperintensities involving the medial temporal and limbic systems and sparing the lateral temporal and insular cortices. Involvement of the basal ganglia is frequently seen, unlike herpes encephalitis which tends to spare the basal ganglia. The presence of hemorrhages on susceptibility-weighted imaging also favors a diagnosis of herpes encephalitis. Treatment requires immune therapy in the form of steroids, intravenous immunoglobulin or plasma exchange, as well as rituximab in refractory cases.

8.7 Conclusion

Acute CNS infections in the neurointensive care are caused by a wide array of microorganisms leading to distinct clinical syndromes such as meningitis, encephalitis, and brain abscess. Rapid and accurate diagnosis and early constitution of aggressive empirical therapy constitute the mainstay of management and are imperative to improve prognosis in these patients.

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Obstetric and Gynecological Infections

9

Puneet Khanna and Velmurugan Selvam

9.1 Introduction

Sepsis is a multisystem disorder caused by dysregulated immune response to infection resulting in multiorgan failure and mortality (Singer et al. 2016). Sepsis is a major health concern for obstetric patients leading to intensive care unit admission and one of the leading causes of maternal mortality worldwide (Moaddab et al. 2016; Say et al. 2014a). Pregnant women have an increased morbidity and mortality for certain illnesses owing to the unique physiological, immunologic, and metabolic changes in pregnancy that complicates management (Mabie and Saibai 1990; Lapinsky et al. 1997). The normal cardiopulmonary changes of pregnancy may mask the clinical signs of sepsis and may go undiagnosed until there is significant clinical deterioration. Timely recognition, adequate source control, and appropriate antimicrobial therapy are responsible for good outcomes in obstetric patients with sepsis. Specific knowledge about pathophysiology and management guidelines of sepsis in pregnancy and puerperium is still lagging. Management of critically ill septic obstetric patients is challenging because of pregnancy-induced physiological changes and it involves care of another life as fetal well-being is dependent on maternal outcome.

9.2 Epidemiology

Globally sepsis is one of the leading causes of maternal mortality contributing to approximately 5% of maternal deaths in developed countries and 11% of maternal deaths in developing nations (Say et al. 2014b). Indian data on obstetric patients with sepsis is lacking. In the USA, mortality from maternal sepsis is 17.2 per

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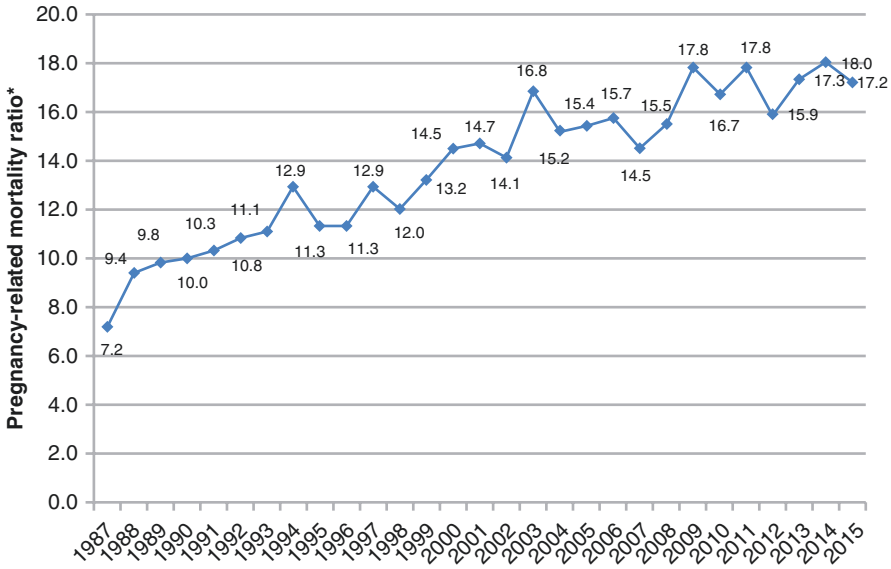

Fig. 9.1 Pregnancy related mortality ratio over years

100,000 live births in 2015 and is steadily increasing over last few years (Fig. 9.1). According to Confidential Enquiries into Maternal Deaths in the UK, sepsis was the leading cause of direct maternal death (Cantwell et al. 2011). In a recent retrospective population-based cohort study which included 1,622,474 live births, incidence of sepsis and severe sepsis was 10 and 4.9 per 10,000 live births. It was also found in the study that approximately 1 in 1000 women giving birth will develop severe infection with a systemic inflammatory response; half of these will progress to sepsis with organ dysfunction and 3–4% to septic shock (Acosta et al. 2013).

9.3 Definitions

In a recent consensus statement by Society of Critical Care Medicine and the Society of European Intensive Care Medicine defined *sepsis* as life-threatening organ dysfunction due to dysregulated host response to infection and patients without organ dysfunction are classified as having an *infection*. *Septic shock* is a subset of sepsis in which patients require vasopressor support to maintain a mean arterial pressure greater than 65 mmHg and have a serum lactate level greater than 2 mmol/L after adequate fluid resuscitation. *Maternal sepsis* (WHO consensus definition) is a life-threatening condition defined as organ dysfunction resulting from infection during pregnancy, childbirth, post-abortion, or the postpartum period. *Puerperal sepsis* is defined as infection of the genital tract which occurs as a complication of delivery. Puerperal pyrexia is considered as genital tract infection unless proven otherwise.

9.4 Causes of Sepsis in Obstetrics

Infections in obstetric population can be due to pregnancy related infections and nonpregnancy related infections (Table 9.1). Some infections can be incidental due to pregnancy like HIV, appendicitis, cholecystitis, disseminated herpes, etc.

The common etiologies of infection during pregnancy are different in the antenatal and postnatal period (Table 9.2). In developing countries, HIV, community acquired pneumonia (streptococcal and influenza), and malaria are most important non-obstetric causes of sepsis.

Pregnancy related physiological changes predispose obstetric population to four specific infectious conditions: urinary tract infection—pyelonephritis, chorioamnionitis (including septic abortion), endometritis, and pneumonia. Loss of ureteral sphincter tone due to pregnancy hormones like progesterone and compression of the urinary system with gravid uterus results in colonization of urinary tract and kidney with Gram-negative bacteria leading to complicated *urinary tract infection and pyelonephritis*. *Pneumonia* can be due to loss of lower esophageal tone due to progesterone and elevation of diaphragm resulting in aspiration of gastric contents. Pregnancy-induced immunosuppression can sometimes lead to fungal and viral pneumonia although rare. Increased glycogen content of the vagina and alteration of vaginal PH leads to loss of the barrier and bacterial entry resulting in *Chorioamnionitis*. Sometimes it can also complicate chorionic villus sampling, amniocentesis, or suction and evacuation following miscarriage. Change in cell mediated immunity and shift from T-helper type 1 cell-mediated immunity to humeral immunity predisposes pregnant patients to certain infections like viral infections and infections by intracellular pathogens.

Table 9.1 Causes of sepsis in obstetrics

Pregnancy related infections	Nonpregnancy related infections
• Chorioamnionitis • Septic abortion • Endometritis • Mastitis • Puerperal sepsis • Septic pelvic thrombophlebitis	• Pneumonia caused by Streptococcus pneumoniae and influenza • Urinary tract—Pyelonephritis • Pelvic abscess • Wound infections and necrotizing fasciitis • Malaria and other tropical illness

Table 9.2 Etiology of obstetric sepsis

Antenatal infections	Postnatal infections
• Chorioamnionitis • Pneumonia caused by Streptococcus pneumoniae and influenza • Urinary tract—Pyelonephritis • Septic abortion	• Common cause—Endometritis • Wound infections • Necrotizing fasciitis • Toxic shock syndrome • Pelvic abscess • Septic pelvic thrombophlebitis

Table 9.3 Microbiology of obstetric infection

Organism	Antenatal (%) (Knowles et al. 2015)	Postnatal (%) (Knowles et al. 2015)
E. coli	55	42
Group B streptococcus	4.2	9.2
Anaerobes	8.5	8.5
Staphylococcus	8.5	9.2
Enterococcus	4.2	4.6
Klebsiella	2	1.5
H. influenzae	6.4	0
Other	11.2	11.2

Table 9.4 Risk factors for obstetric sepsis

Obesity factors	Patient factors
• Amniocentesis and other invasive intrauterine procedures • Cervical suture • Prolonged rupture of membranes • Prolonged labor with multiple (>5) vaginal examinations • Vaginal trauma • Cesarean section • Retained products of conception after miscarriage or delivery	• Obesity • Impaired glucose tolerance/diabetes • Impaired immunity • Anemia • Malnutrition • Poor socioeconomic status • Vaginal discharge • History of pelvic infection • History of group B streptococcal infection

9.5 Microbiology of Obstetric Infection

In developing countries like India, limited data regarding the specific microbial cause of obstetric infections is lacking. Data from developed countries showed that most of the obstetric infections are polymicrobial in nature caused by organisms colonizing the female genital tract. E. coli is the most common organism isolated in pregnancy related infections (Table 9.3). Over recent years, there has been significant increase in serious diseases caused by group A streptococci (GAS) like fulminant toxic shock syndrome and necrotizing fasciitis. The risk factors for developing maternal sepsis are broadly classified into patient related and obstetric factors (Table 9.4).

9.6 Recognizing Infection/Sepsis in Obstetric Patients

Sepsis is a syndrome and diagnosis is mostly clinical as microbiological tests and biomarkers can often be negative. Diagnosis of infection and sepsis can be difficult during pregnancy and puerperium due to non-specific presentation and resemblance of symptoms to normal physiological changes of pregnancy. This can lead to

delayed diagnosis and worse clinical outcome. So, clinician should have high index of suspicion for diagnosis of sepsis in obstetric patients. The sepsis-3 definition recommends a screening test, the Quick Sequential Organ Failure (qSOFA) assessment to identify patients with sepsis. Sepsis should be considered in any patient if two of the following three criteria are present:

1. Altered mentation.
2. Respiratory rate of greater than or equal to 22/min.
3. Systolic blood pressure of less than or equal to 100 mmHg.

If qSOFA is ≥2, then the physician should promptly investigate for the presence or absence of organ dysfunction by SOFA score (consider sepsis if SOFA score increases by ≥2 points). However, these scoring systems have not been adjusted for physiological changes of pregnancy leading to underdiagnosis/overdiagnosis of sepsis. Therefore, these scoring systems may assist the clinician but do not replace clinical judgment.

Several pregnancy specific scoring systems have been developed to identify patients at risk and to decrease morbidity and mortality. One such scoring system is *Sepsis in Obstetrics Score* (Table 9.5) and may have utility to identify patients with risk for ICU admission. With score of ≥6, the S.O.S. had a sensitivity of 88.9%, a specificity of 95.2%, a PPV of 16.7%, and an NPV of 99.9% for ICU admissions.

Table 9.5 Sepsis in obstetrics score

Variable	High abnormal range				Normal	Low abnormal range			
score	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature (°C)	Higher than 40.9	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	Less than 30
Systolic blood pressure (mmHg)					Higher than 90		70–90		Less than 70
Heart rate (beats per minute)	Higher than 179	150–179	130–149	120–129	119 or less				
Respiratory rate (breaths per minute)	Higher than 49	35–49		25–34	12–24	10–11	6–9		5 or less
SpO_2 (%)					92% or higher	90–91%		85–89%	Less than 85%
White blood cell count (/μL)	Higher than 39.9		25–39.9	17–24.9	5.7–16.9	3–5.6	1–2.9		Less than 1
% immature neutrophils			10 or higher		Less than 10				
Lactic acid (mmol/L)			4 or higher		Less than 4				

An S.O.S ≥6 was independently associated with increased ICU admissions, positive blood cultures, and fetal tachycardia (Albright et al. 2014).

9.7 Maternal Early Warning Scores

Early warning scores (EWS) have been in use since 1999 to identify patients at risk of deterioration and to decrease morbidity and mortality. Due to normal physiological changes of pregnancy, the EWS for the non-obstetric population cannot be used to the obstetric population. The maternal early warning score (MEWS) was developed to improve early identification of pregnant women at risk of clinical deterioration and facilitate early intervention (Table 9.6) (Knight et al. 2016). The parameters commonly included in MEWS are heart rate, respiratory rate, blood pressure, and level of consciousness (Table 9.1). Sometimes other parameters such as the pain score, lochia characteristics, and urine output are also included. Many variations of obstetric EWSs such as the Modified Obstetric Early Warning System (MOEWS), the Maternal Early Warning Trigger tool (MEWT), and the Irish Maternal Early Warning System (IMEWS) are also available.

The National Partnership for Maternal Safety developed maternal early warning criteria (Table 9.7) which includes bedside evaluation of vital sign parameters by the clinician care escalation as needed (Mhyre et al. 2014).

Table 9.6 Maternal early warning score

Physiological parameters	Normal values	Yellow alert	Red alert
Respirator rate	10–20 breaths per min	21–30 breaths per min	<10 or >30 breaths per min
Oxygen saturation	96–100%		<95%
Temperature	36.0–37.4 °C	35–36 or 37.5–38 °C	<35 or >38 °C
Systolic blood pressure	100–139 mmHg	150–180 or 90–100 mmHg	>180 or <90 mmHg
Diastolic blood pressure	50–89 mmHg	90–100 mmHg	>100 mmHg
Heart rate	50–99 beats per min	100–120 or 40–50 beats per min	>120 or <40 beats per min
Neurological response	Alert	Voice	Unresponsive, pain

Table 9.7 Maternal early warning criteria

Systolic BP (mm Hg) <90 or >160
Diastolic BP (mm Hg) >100
Heart rate (beats per min) <50 or >120
Respiratory rate (breaths per min) <10 or >30
Oliguria, <35 mL/h for 2 h
Maternal agitation, confusion, or unresponsiveness
Patient with preeclampsia reporting a non-remitting headache or shortness of breath
Oxygen saturation on room air, at sea level <95%

9.8 Management of Sepsis in Obstetric Patients

Despite increasing knowledge about pathogenesis and management of sepsis in last two decades, specific knowledge about management of sepsis in obstetric patients is still lagging. Management of sepsis in an obstetric patient involves taking care of both the mother and child. Since uteroplacental circulation does not have autoregulation, any hemodynamic instability of mother results in fetal hypoxia and acidemia. Effective maternal resuscitation is the cornerstone for optimizing fetal well-being.

9.9 Initial Resuscitation

Although there are no prospective studies of early goal-directed therapy during pregnancy, the management of sepsis should be similar to that of the nonpregnant patient and use the same targets. RCOG also has suggested the management of sepsis in obstetrics in accordance with the Surviving Sepsis (SS) Campaign guidelines. In 2018 update of surviving sepsis campaign bundle, 3-h and 1-h bundles have been combined into a single "Hour-1 bundle" (Table 9.8).

9.10 Fluid and Hemodynamic Support

Fluid resuscitation is essential in the early phases of shock, particularly in cases of sepsis. Surviving Sepsis Campaign guidelines (2012) recommend infusion of 30 mL/kg (fixed volume) of crystalloids within the first hour immediately after the diagnosis of septic shock (Rhodes et al. 2017). However, individualized strategy of fluid management in sepsis had been shown to improve outcomes in several clinical trials (Hernández and Teboul 2017; Jozwiak et al. 2018). The main goal of fluid administration is to increase the venous return and ultimately to improve cardiac output and oxygen delivery to the tissues. Fluid administration will lead to increase in cardiac output only if the preload of both ventricles operates on the ascending portion of the frank starling curve. If the preload of the ventricles operates on the flat portion of the frank starling curve, then volume expansion may only exert adverse effects leading to pulmonary edema without increase in cardiac output or any hemodynamic benefit. Obstetric patients are at high risk of pulmonary edema because of low plasma oncotic pressure.

Table 9.8 Hour-1 SSC bundle of care

- Measure lactate level. Remeasure lactate if initial lactate is elevated (> 2 mmol/L)
- Obtain blood cultures before administering antibiotics
- Administer broad-spectrum antibiotics
- Begin rapid administration of 30 mL/kg crystalloid for hypotension or lactate level ≥4 mmol/L
- Apply vasopressors if hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg

Only 50% of patients with septic shock respond to fluid. Fluid responsiveness should be assessed before volume expansion to avoid volume overload and its complications. Recent evidence shows that various dynamic parameters (both invasive and non-invasive) have a high sensitivity and specificity for predicting fluid responsiveness compared to static markers (CVP, PAOP, and LVEDV). These dynamic parameters include pulse pressure variation (PPV), systolic pressure variation (SPV), stroke volume variation (SVV), aortic peak velocity variation, and velocity time integral variation (VTI) (Mallat et al. 2015; Miller and Mandeville 2016; Muller et al. 2011). Mini fluid challenge and end expiratory occlusion test are other fluid responsive tests that have got very good predictability for assessing fluid responsiveness in whom dynamic markers cannot be used (not in sinus rhythm, spontaneous breathing effort) (Monnet et al. 2016; He and Liu 2016).

9.11 Antibiotic and Source Control

Early recognition of source of sepsis and aggressive strategies to eradicate the source are of utmost importance in management of sepsis. Antibiotic therapy via the intravenous route and in appropriate therapeutic doses should be started as early as possible within the first hour of hypotension. In a cohort study of more than 2700 adults (nonpregnant) admitted with septic shock, the interval between onset of hypotension and administration of effective antibiotic treatment was inversely proportional to survival (Kumar et al. 2006). Every hour delay in administration of antibiotic during first 6 h after recognition of hypotension resulted in 7.9% increased mortality.

The initial choice of antibiotic is empiric and broad for unknown source of sepsis decided by the prevalence and susceptibility patterns in the hospital. If the source is known, specific antimicrobial regimens should be used per guidelines or hospital protocol (e.g., community-acquired pneumonia, influenza, urinary tract infection, etc.). Group A streptococcus and Escherichia coli are the most common causes of obstetric sepsis, and empirical coverage should include these organisms (Table 9.9). Antibiotic therapy should be narrowed/de-escalated as soon as causal organism and its susceptibility pattern are identified (Paruk 2008). Dosing strategies of antibiotics should be based on pharmacokinetic and pharmacodynamic principles. Initial doses of antibiotics in obstetric patients are often insufficient due to an increase in volume

Table 9.9 Suggested initial intravenous antibiotic therapy in obstetric sepsis

- Piperacillin–tazobactam 4.5 g 8 hourly or ciprofloxacin 600 mg 12 hourly plus gentamicin 5–7 mg/kg daily in divided doses every 8 hours.
- A carbapenem such as meropenem 500 mg to 1 g 8 hourly ± gentamicin.
- Metronidazole 500 mg 8 hourly may be considered to provide anaerobic cover.
- If group A streptococcal infection is suspected, clindamycin 600 mg to 1.2 g three or four times daily to inhibit exotoxin production.
- If there are risk factors for MRSA septicemia, add teicoplanin 10 mg/kg 12 hourly for three doses, then 10 mg/kg 24 hourly or linezolid 600 mg 12 hourly.

of distribution and augmented renal clearance two physiological changes invoked by pregnancy (Roberts et al. 2014). US FDA categorized drugs used in pregnancy into five categories based on fetal risk. Among the most commonly used antibiotics, aminoglycosides and tetracyclines are included in category D and should be avoided in early pregnancy. Source control is an important component of sepsis management. Diagnostic imaging is often helpful confirming source of infection and is often amenable to source control. Source control is especially crucial in septic abortion. In case of abdominal or pelvic abscess, minimally invasive procedure like percutaneous drainage is preferred over laparotomy.

9.12 Fetal Considerations

Feto-placental circulation does not have autoregulation; any hemodynamic compromise of the mother will affect fetal well-being. Maintenance of adequate cardiac output and oxygenation are important for fetal well-being. Continuous fetal monitoring should be considered in obstetric sepsis beyond gestational age at which fetal survival is possible (usually 20 weeks). Attempts for delivery of the fetus should be delayed until maternal condition is stabilized. Delivery before maternal stabilization increases both maternal and mortality unless intrauterine infection is considered as a source of infection (septic abortion, chorioamnionitis).

9.13 Conclusion

Owing to the unique physiological, immunologic, and metabolic changes, pregnant patients are at risk of certain infections. Obstetric sepsis remains major cause of maternal ICU admission and one of the leading causes of maternal morbidity and mortality. Timely recognition, adequate source control, and appropriate antimicrobial therapy are responsible for good outcomes in obstetric patients with sepsis.

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Surgical Infections in ICU

10

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Surgical infections cover a broad spectrum of infections involving various organ systems and are caused by various organisms. The common feature of all surgical infections is that they may require surgical treatment, a process called "source control". These infections are essentially caused by violation of an epithelial barrier by surgery, trauma or any endogenous pathology like ischaemia, obstruction, etc. Thus, the term "surgical infection" encompasses all pathologies, from a minor wound infection to fatal infections like necrotizing fasciitis or bowel gangrene. Depending on the type of infection, the "source control" can be as simple as just removal of a suture to drain an infected wound, to extensive debridement or organ resection.

Surgical patients are particularly susceptible to hospital acquired infections (HAI). Thus, the spectrum of surgical infections has now been widened to include any infection that affects surgical patients. Certain infections are more common in an intensive care setting, and these will be the focus of this chapter. Surgical infections in intensive care unit (ICU) patients are encountered in two settings. Either these patients are admitted in ICU with an infection (usually post-operative) or they develop the infection during ICU stay for a different disease.

10.1 Epidemiology

In a study by Markogiannakis et al, 18% of patients in a surgical ICU (SICU) of a university hospital in Greece suffered from some infection. These included bloodstream infections (46%), ventilator associated pneumonia (25%), surgical site infection (19%) and urinary tract infections (9%) (Markogiannakis et al. 2009). In an

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Indian study, the incidence of nosocomial infection was 33.3%. Skin and soft tissue infections (36.3%), including surgical site infections (SSI), were most common, followed by respiratory tract infections (24.5%) and genitourinary infections (23.4%). Common pathogens were *E. coli* (26.6%) and *Acinetobacter* (18.1%). Nosocomial infections caused a significant increase in mortality in SICU patients (Baviskar et al. 2019).

10.2 Surgical Site Infections

Surgical site infections (SSI) constitute one of the most common complications in SICU patients. Any surgical incision creates a portal of entry for microorganisms. An immunocompetent person would mount an adequate immune response to prevent an infection. However, surgery itself causes immunosuppression which is more pronounced in trauma, burn, malignancy and in patients undergoing transplant. High prevalence of various nosocomial infections in the ICU further adds to the risk of SSI.

SSI can be categorized as superficial incisional SSI (involving skin and subcutaneous tissue only), deep incisional SSI (involving fascia and muscle layers) and organ space SSI (involving internal organs that have been manipulated during surgery). The source of the infecting organism can be endogenous (e.g. when the wound is contaminated by contents from a hollow viscus) or exogenous (e.g. wound contamination by a break in asepsis). In a recent study, the common organisms causing SSI in the SICU were *E. coli, Pseudomonas aeruginosa and Candida albicans* (Ballus et al. 2015). This is in contrast to the flora seen in SSI in the general ward, where Gram positive cocci like *Staphylococcus aureus* and *Staphylococcus epidermidis* are more commonly isolated from wound infections.

10.2.1 MRSA

Superficial SSI is diagnosed clinically by the presence of local erythema, induration, rise of temperature and tenderness, with or without discharge of pus. Pus cultures are not essential for diagnosis, as simple opening of the incision and drainage of the pus usually is adequate treatment. Antibiotic therapy is required when erythema extends beyond the margins of the incision. Deep incisional SSI may cause more diffuse tenderness beyond the margin of erythema, crepitus, cutaneous vesicles or bullae. Organ space SSI cause symptoms specific to the involved organ or space like ileus, diarrhoea, dyspnoea, etc. Systemic features like fever, tachycardia, tachypnoea and leucocytosis are indicators of sepsis and are more commonly associated with deep incisional and organ space SSI. Deep incisional SSI may require surgical debridement. Organ space infections, if suspected, should be confirmed by imaging like ultrasound or CT scan. Source control is done by percutaneous or formal surgical drainage. For deeper SSI, antibiotics should be started empirically and cultures sent for more targeted therapy.

10.2.2 Necrotizing Soft Tissue Infections

These are rapidly spreading infections, which may manifest as early as 24–48 h post-operatively, in contrast to other SSI that become clinically apparent 4–5 days after surgery. These include gas gangrene (caused by *Clostridium perfringens*), type I necrotizing fasciitis (polymicrobial) and type II necrotizing fasciitis (group A *Streptococcus*). Polymicrobial infections involving the perineum are referred to as Fournier's gangrene. The condition may be fatal if not detected and treated urgently. Incisional pain along with cutaneous blebs or bullae, crepitus, cutaneous anaesthesia and signs of cellulitis, although pathognomonic, are present in less than half the cases. Tenderness beyond the margins of cellulitis and systemic signs of sepsis and leucocytosis should raise suspicion. Emergent surgical debridement and broad-spectrum antibiotic coverage (penicillin, clindamycin and aminoglycoside) are the cornerstone of therapy. Frequent wound assessment and serial debridement are needed when extension of the infective process occurs.

10.3 Pressure Sores

In spite of good nursing care, up to 23% of ICU patients develop pressure ulcers, most commonly over the sacrum, calcaneum, greater trochanter and ears (Becker et al. 2017; Krupp and Monfre 2015). Pressure sores may be classified as stage I (intact skin with localized redness that does not blanch with light pressure), stage II (shallow ulcer with red or pink floor, due to partial loss of thickness of dermis), stage III (full thickness loss of dermis leading to visible subcutaneous fat) and stage IV (exposed bone, tendon or muscle). Some pressure sores may be unstageable due to the presence of slough or eschar over an area of tissue loss, or may have an intact, albeit discoloured skin, due to damage of underlying tissues (Estilo et al. 2012). Pressure sores may be preventable to a large extent by 2 hourly position change, use of air mattresses, use of lift teams and equipments, etc. Once a pressure sore is detected, moist occlusive dressing of the ulcer is recommended. Various dressing materials like hydrocolloid, hydrogel, polymers, alginates and biomembranes have been proposed. Surgical debridement is necessary in the presence of necrotic tissue. Vacuum assisted devices may be applied for wound management after debridement. Improvement of nutrition is a vital component in the healing of wounds. Protein supplements enriched with arginine, zinc and vitamin C have been suggested to promote wound healing.

10.4 Intra-Abdominal Infections

Intra-abdominal infection (IAI) can arise after any abdominal surgery, which is referred to as organ/space infection, or may occur de novo, as in any infective process involving the abdominal organs, e.g. appendicitis, liver abscess, diverticulitis, etc. About 30% of patients with IAI admitted in ICU die due to their illness (Evans

et al. 2001; Bohnen et al. 1983). When IAI occurs as a post-operative complication or recurs during ICU admission, mortality is even higher (Nathens et al. 1998).

Intra-abdominal infections result in infection of peritoneal fluid or peritonitis, which is classified as primary, secondary and tertiary peritonitis. Primary peritonitis or spontaneous bacterial peritonitis (SBP) occurs in the absence of a breach of the gastrointestinal tract. It is most commonly seen in decompensated cirrhosis. Bacterial translocation through an intact bowel wall, probably due to abnormal overgrowth of organisms in the proximal small bowel, is considered as an important step in the pathogenesis of SBP (Cirera et al. 2001). Typically, the infection is monomicrobial, with Gram negative enteric bacilli and enterococci being the most common isolates. SBP in ICU patients is often caused by Gram positive cocci (Fernández et al. 2002). Diagnosis of SBP can be established by culture of peritoneal fluid. However, empirical management with broad-spectrum antibiotics is started when ascitic fluid cytology shows more than 250 neutrophils/mm^3 in a clinical setting consistent with SBP (abdominal pain, fever or leucocytosis in a patient with low protein ascites). SBP is rarely found in high protein ascites; a low level of protein in ascitic fluid prevents effective opsonization of bacteria and clearance by macrophages and neutrophils. Once culture sensitivity reports are available, antibiotic therapy is tailored. Thuluvath et al., in a study of 348 patients, found an in-hospital mortality of 32.6%; patients in ICU had a 2.8 times higher likelihood of death (Thuluvath et al. 2001).

Secondary peritonitis occurs due to a breach in the integrity of the bowel wall, e.g. a perforated ulcer or diverticulum, anastomotic leak or a traumatic perforation. Unlike SBP, the infection is polymicrobial. Secondary peritonitis can occur in cirrhotic patients as well; a polymicrobial culture or presence of anaerobes is suggestive of secondary peritonitis (Akriviadis and Runyon 1990). Generally, proximal small bowel perforations are associated with Gram negative organism infections, while anaerobic infections are found in distal small bowel or colonic perforations. Clinically, patients present with abdominal pain and tenderness. Diffuse pain is suggestive of generalized peritonitis, which is usually seen with Gram negative aerobic infections. Localized pain is found when the infection is walled off by an abscess, typically seen in anaerobic infections. Although in young, otherwise healthy patients, the diagnosis is quite straightforward, elderly and immunocompromised patients may present with diagnostic uncertainty, due to masking of signs. In unconscious or sedated patients (e.g. ventilated patients in ICU) the only evidence of such an infection may be an unexplained leucocytosis or a sudden organ system dysfunction.

Tertiary peritonitis is typically seen in critically ill patients, where peritonitis is found to persist or recur at least 48 h after adequate management of primary or secondary peritonitis. The causative organisms of tertiary peritonitis are different from those causing secondary peritonitis and are generally unresponsive to antibiotics and source control measures. These include coagulase negative *Staphylococcus, Pseudomonas, Candida* and enterococcus (Nathens et al. 1998).

Clinically, IAI presents with unexplained development of organ system dysfunction, e.g. shortness of breath, hypotension or supraventricular dysrhythmias, acute

kidney injury, deranged liver function or unexplained metabolic acidosis. Blood cultures may be negative. In fact, a negative blood culture actually increases the likelihood of an IAI (Le Gall et al. 1982).

When IAI is suspected, diagnosis is confirmed by imaging. Plain X-ray abdomen may reveal intraperitoneal free air, dilated bowel loops or multiple air-fluid levels suggestive of obstruction. Contrast enhanced CT scan is the imaging modality of choice in critically ill patients (Velmahos et al. 1999). Findings suggestive of infection are air within a collection, heterogeneity and rim enhancement. Oedema and mesenteric fat stranding suggest inflammation. Extraluminal contrast may be seen in anastomotic leak. Ischaemia is characterized by non-enhancement of tissues, air within the wall of the bowel (pneumatosis) and within mesenteric vessels. Use of contrast should be avoided, if possible, in patients with renal dysfunction. If the benefits outweigh the risks, however, contrast may be administered after proper hydration and pre-medication with n-acetyl cysteine, 600 mg twice daily (Tepel et al. 2000).

Ultrasound has the advantage of being portable and more easily available and is often the first imaging investigation done on ICU patients, especially patients on ventilator, shifting whom to the CT gantry can be difficult (Marshall et al. 1993). However, it is operator dependent and difficult to perform in patients with large dressings or paralytic ileus. If a collection is detected on ultrasound, USG guided aspiration or pigtail drainage may be done. However, in the absence of any collection on ultrasound in a suspected patient, CT scan must be done as it has higher sensitivity for detection of intra-abdominal collection.

Diagnostic peritoneal lavage (DPL) may be a useful tool in very sick patients who are deemed unfit for anaesthesia or are too unstable to be shifted for imaging. Ultrasound guided or blind DPL may reveal bacteria or pus cells, bile or intestinal contents (Alverdy et al. 1988). In unstable patients with secondary peritonitis, placement of drains under local anaesthesia is both diagnostic and therapeutic, in that it may improve ventilation.

10.5 Management

The initial management in IAI is airway stabilization, if indicated, followed by fluid resuscitation. Substantial quantity of fluids may need to be administered depending on the volume of third space loss. Urine output of 0.5–1 mL/kg/h is a good indicator of adequate fluid resuscitation. In patients with cardiovascular disease, a central line should be placed to better monitor fluid balance. A blood culture should be sent before starting broad-spectrum empirical antibiotics, which should cover Gram negative aerobes and anaerobes, when the source of contamination is not known. If the infection is known to arise from the upper gastrointestinal tract (e.g. perforated duodenal ulcer) anaerobic coverage is not necessary (Nathens and Rotstein 1994).

Once the patient is stable, attention should be directed towards source control, i.e. eradication of the focus of infection, prevention of ongoing contamination and restoration of optimal anatomy and function (Jimenez et al. 2001). Source control

measures are based on three principles—drainage, debridement and definitive management.

10.5.1 Drainage

Inflammatory response to IAI results in deposition of fibrin and formation of an abscess—a collection of necrotic tissue, bacteria, neutrophils, macrophages and protein-rich exudative fluid enclosed within a fibrous capsule. Abscess formation is the body's innate response in order to prevent infection from affecting surrounding healthy tissues. The disadvantage of abscess formation is that it prevents the further entry of host cells or antibiotics to the site of infection. Drainage converts an abscess into a controlled sinus (external drainage) or fistula (internal drainage, e.g. cystogastrostomy in walled off necrosis of pancreas). Most intra-abdominal abscesses can be managed by image guided percutaneous drainage (van Sonnenberg et al. 2001). Surgical drainage is indicated when percutaneous drainage fails, when there is significant solid debris in the abscess cavity, for simultaneous management of the source of ongoing contamination (e.g. perforated peptic ulcer), multiple abscesses or abscess in difficult anatomical position, and generalized peritonitis.

10.5.2 Debridement

While drainage eliminates the liquid component of an infection, solid necrotic tissue requires surgical debridement. Examples include pancreatic necrosectomy, removal of faeces or intestinal contents from peritoneal cavity in patients with intestinal perforation, resection of gangrenous bowel or excision of necrotic abdominal wall muscles in necrotizing soft tissue infection. The timing of interval is highly variable depending on the disease; e.g. in mesenteric ischaemia, early intervention and resection of gangrenous bowel is required as the leakage of bacteria through bowel wall is considerable (Schein and Marshall 2002). In contrast, in infected pancreatic necrosis, debridement is delayed, as early retroperitoneal exploration is associated with increased risk of bleeding and mortality due to poor demarcation of viable and non-viable tissue (Mier et al. 1997).

10.5.3 Definitive Measures

Definitive management includes measures to remove foci of ongoing contamination and restoration of normal structure and function. All of these may not be possible in every patient of IAI. For example, in critically ill patients with acute cholecystitis (Tokyo Grade III), simple drainage of gallbladder bile by percutaneous cholecystostomy is recommended and definitive management by cholecystectomy is deferred till the patient recovers (Boggi et al. 1999). In patients with bowel sigmoid diverticular perforation, sigmoidectomy should be done (Jimenez et al. 2001) but

restoration of bowel continuity by colorectal anastomosis in the same sitting depends on multiple factors like general condition of the patient, degree of peritoneal contamination, bowel oedema, etc. Young patients who present with secondary peritonitis within 6–12 h are good candidates for anastomosis. In the presence of adverse factors like haemodynamically unstable patients, bowel, oedema, etc., creation of a stoma is recommended. Stomas should be planned and positioned keeping in mind the possibility of an open wound and also such that the magnitude of surgery required for subsequent closure is as less as possible. For example, when multiple segmental bowel resections are performed, especially involving the colon, it is preferable to reconstruct the distal gastrointestinal tract and create a proximal loop ileostomy, which can be closed locally without midline laparotomy. Abdominal closure may not be possible in patients with severe bowel oedema or extensive loss of abdominal wall tissue due to necrotizing infection. However, there is no evidence to support prophylactic open abdomen approach when fascial closure can be done without undue increase in intra-abdominal pressure (Lamme et al. 2002).

Source control and appropriate antibiotic therapy can lead to resolution of inflammation and reversal of organ dysfunction in patients with IAI. The management of IAI in critically ill patients is complex, challenging, costly and at times, frustrating. However, long-term quality of life in survivors is very good (Scheingraber et al. 2002) and cost per quality-adjusted life years is favourable, which justify the efforts and expenses that have to be put in managing this complex patient population.

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Skin and Soft Tissue Infections in ICU

11

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11.1 Introduction

Skin and soft tissue infections (SSTIs) encompass various infectious conditions involving the skin, subcutaneous layer, fascia, and muscle layer. Lower extremities and perineum are most commonly involved but any part of the body may be involved. Patients with uncomplicated superficial SSTIs are treated as outpatients and are rarely encountered in intensive care settings. Surgical infections, necrotizing infections, or complicated infections with systemic features of toxemia or sepsis are of relevance in intensive care settings.

11.2 Classification

Several classification systems have been proposed for SSTIs. The most notable ones are listed below:

1. The US Food and Drug Administration (FDA) classification (Sartelli et al. 2014):
   a. Uncomplicated SSTIs are superficial, and are at low risk of life or limb threatening infections. They require minimal surgical interventions limited to incision and drainage.
   b. Complicated infections involve deep tissues and require extensive surgical explorations for treatment.
2. The World Society of Emergency Surgery classification (Sartelli et al. 2014):
   a. Surgical site infections
      - Superficial incisional
      - Deep incisional

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b. Non-necrotizing SSTIs
   - Superficial (impetigo, erysipelas, cellulitis)
   - Simple abscess, boils, and carbuncles
   - Complex abscesses

c. Necrotizing SSTIs (NSTIs)
   - Necrotizing cellulitis
   - Necrotizing fasciitis
   - Necrotizing gangrene
   - Necrotizing myositis

3. The classification proposed by the Infectious Diseases Society of America (IDSA) in their practice guidelines for the diagnosis and treatment of SSTIs (Stevens et al. 2014):
   a. Superficial uncomplicated infections: Impetigo, erysipelas, cellulitis.
   b. Necrotizing soft tissue infections (NSTIs).
   c. Infections associated with bite wounds and animal contacts.
   d. Surgical site infections.
   e. Infections in the immunocompromised host.

11.2.1 Superficial Uncomplicated SSTIs

11.2.1.1 Impetigo and Ecthyma

Impetigo is a bacterial infection involving the epidermis of the skin. It is predominantly seen in children aged 2–5 years but may present in older children and adults (Hirschmann 2002). It presents most commonly as non-bullous honey crusted lesions, or less commonly as bullous lesions. Most common causative organisms of non-bullous impetigo are *S. aureus,* streptococci, or their combination. Bullous impetigo is caused by *S. aureus* strains that release toxins that cleave the dermo-epidermal junction (Amagai et al. 2000). Streptococcal impetigo can lead to sequelae such as post-streptococcal glomerulonephritis or rheumatic fever. Ecthyma is a punched out form of streptococcal impetigo that involves dermis and heals with scarring.

Topical treatment with mupirocin or retapamulin is sufficient in cases with limited number of lesions and oral antibiotic may be used in case of widespread lesions or in outbreaks to decrease the rate of transmission (Stevens et al. 2014). Empiric antibiotics should be effective against both *S. aureus* and *S. pyogenes*. Cephalexin or dicloxacillin are the usual choices (Stevens et al. 2014). Alternative treatment with trimethoprim-sulfamethoxazole, clindamycin, linezolid, or fluoroquinolones should be considered in penicillin allergy or MRSA infections.

11.2.1.2 Erysipelas and Cellulitis

Erysipelas is nonpurulent bacterial infection of superficial dermis and lymphatics presenting as well-demarcated raised erythematous plaques. Cellulitis involves the deeper dermis and subcutaneous fat, and may present with or without purulence. Cellulitis and erysipelas present with local signs of inflammation, such as erythema, tenderness, lymphangitis and warmth, with or without systemic symptoms like

fever, tachycardia, and raised leucocyte counts. Erysipelas and cellulitis are caused by the entry of microbes through breach in skin. In most cases, the offending organisms are streptococci with only a small proportion of cases, mostly in open wound or previous penetrating injury, caused by *S. aureus*. Treatment involves antibiotic therapy targeting streptococci and MSSA, such as penicillins, first or second generation cephalosporins, or clindamycin. Antibiotics active against MRSA (vancomycin, daptomycin, linezolid) may be considered in cellulitis associated with penetrating trauma, illicit drug use, purulent drainage, or with concurrent evidence of MRSA infection elsewhere. The affected limb should be elevated to facilitate gravity drainage of edema (Stevens et al. 2014).

11.2.1.3 Cutaneous Abscess

Cutaneous abscesses are collections of pus in dermis and underlying subcutaneous tissue. They present as tender and erythematous fluctuant nodules with varying degree of surrounding cellulitis. It is usually of polymicrobial etiology (Brook and Frazier 1990). Treatment is incision and drainage of pus and exploration of cavity to break all loculations. Packing of the cavity with gauze may be done, although its usefulness in wound healing has not been demonstrated (O'Malley et al. 2009). Antibiotics are to be considered in the presence of systemic features of infection or in immunocompromised patients.

Although the 2014 IDSA guidelines on management of skin and soft tissue infections do not recommend routine use of antibiotic therapy as adjunct to incision and drainage of uncomplicated abscesses, multiple randomized placebo controlled trials have demonstrated improved clinical cure and/or decreased recurrences with empiric adjunctive antibiotics active against MRSA (Stevens et al. 2014; Talan et al. 2016, 2018; Daum et al. 2017; Schmitz et al. 2010). Two recent meta-analyses have found improved cure rates and decreased recurrence of uncomplicated skin abscesses treated with TMP-SMX or clindamycin compared to placebo at the cost of higher incidence of minor adverse effects (Gottlieb et al. 2018; Wang et al. 2018).

11.2.1.4 Folliculitis, Furuncles and Carbuncles

Folliculitis and furuncle are infections of the hair follicle and the pilosebaceous gland, respectively. Folliculitis is a superficial infection with purulent material confined to epidermis. It appears as small red or white spots at the base of the hair follicle. There are usually no systemic manifestations and treatment is with topical antibiotics. Furuncle extends deep into the subcutaneous tissue and present as inflammatory nodules with overlying pustules. Infections of several adjacent follicles coalesce to form carbuncle with purulent discharge from multiple follicles. While most smaller furuncles drain spontaneously with moist heat, larger furuncles and carbuncles are treated with incision and drainage followed by regular dressing. Antibiotic therapy active against *S. aureus* is reserved for patients with features of systemic inflammation.

11.2.1.5 Necrotizing Fasciitis

Necrotizing fasciitis (NF) is a rapidly progressive necrotizing infection of superficial fascia of muscles and the overlying subcutaneous fat. NF is included into the broad

category of necrotizing soft tissue infections (NSTIs) that involve varied depth of subcutaneous tissue from dermis down to the muscle layer. The hallmark of NSTI is rapidly progressive and extensive necrosis of subcutaneous tissue. Although the clinical features of necrotizing fasciitis and other NSTIs are similar, the predisposing factors and causative organisms vary. This, however, is of little clinical significance because the principle of management remains essentially the same. NF spreads along the fascia due to its poor blood supply. The rapidity of progression of the infection and the relative lack of specific clinical features early in disease are challenges in the way of preventing mortality or amputation in patients with NF.

11.3 Epidemiology

NF is an uncommon disease with an annual incidence of 0.3–5 cases per 1,00,000 in developed nations (Stevens and Bryant 2017) and higher in south-east Asian nations (Khamnuan et al. 2015; Hung et al. 2014). It is a potentially fatal disease with a high mortality rate of 20–30% (Wong et al. 2003; Rajput et al. 2008; Simsek Celik et al. 2011).

11.4 Etiopathogenesis

NF is caused by an inoculum of pathogenic microorganisms through a breach in the integrity of skin in susceptible individuals, resulting in rapid spread of infection along the fascia. As the infection spreads, the penetrating cutaneous vessels get thrombosed leading to necrosis of overlying tissue. Reported antecedent events range from major trauma, surgery to minor injuries such as insect bites and drug injections. However, a significant number of cases (15–52%) have been reported without any antecedent cause (Gamelli and Posluszny Jr 2012).

The most common risk factors for the development of NF and other NSTIs are as follows:

- Old age
- Diabetes mellitus
- Peripheral vascular disease
- Liver cirrhosis
- IV drug abuse
- Malignancy
- Immunosuppression
- Use of NSAIDs

Based on causative organisms involved, NF may be classified as:

- *Type I (Polymicrobial)*: This is the most common type seen usually in older individuals with comorbidities. The infection involves aerobic and anaerobic organ-

isms and is often associated with gas formation. *Fournier's gangrene* is a subtype of type I NF involving perineum and genitalia and perianal areas which may spread to abdomen due to continuity of Scarpa fascia and Colles fascia.

- *Type II (Monomicrobial)*: These infections are most commonly caused by Group-A β-hemolytic streptococcus (GAS) followed by *S. aureus (*Wong et al. 2003*)*. Type II NF may occur in patients of any age group without any comorbidity.
- *Type III*: Monomicrobial infections caused by Clostridium or gram negative bacteria such as *Vibrio* spp. and *Aeromonas* spp. are often referred to as Type III NF (Stevens and Bryant 2017). These bacteria are seen in warmer marine climate.
- *Type IV*: These are extremely rare fungal infections seen in immunocompromised patients involving *Candida* or *Zygomycetes*.

11.5 Clinical Features

Necrotizing infections most commonly involve the extremities and perineum, but may involve any site. NF is difficult to diagnose due to absence of specific clinical features. The severity of pain is frequently out of proportion to physical findings. The affected area is warm to touch, tender, erythematous, swollen with "dishwater exudation" initially and progresses to develop blue-gray patches, bullae and necrosis. Type I NF may be associated with gas production and crepitus on palpation. As the disease progresses, thrombosis of cutaneous blood vessels and destruction of nerves lead to anesthesia of the skin.

The local findings are accompanied by features of systemic toxemia and sepsis. Fever, malaise, nausea and vomiting, diarrhea, altered mentation is followed by circulatory shock without timely intervention. GAS infection may lead to a clinical picture of fever, anorexia, nausea, vomiting, and diarrhea and features of SIRS early in the disease without early cutaneous manifestations in patients without obvious portal of entry, further complicating the diagnosis. In such cases, pain without obvious cutaneous picture should be picked up as an important clue and diagnostic workup should follow for timely surgical exploration.

11.6 Diagnosis

Surgical exploration with tissue sampling is the definitive method of diagnosing NF. Blood culture, serum biochemistry, and radiological investigations aid in diagnosis. Wong and colleagues have developed a diagnostic scoring system for clinical detection of early NF (Wong et al. 2004). The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score includes C-reactive protein, total leucocyte count, hemoglobin, serum sodium, glucose, and creatinine. The maximum score is 13, and a score of 6 or above should raise the suspicion of NF. A recent meta-analysis has found a mean LRINEC score of 6.06 in patients with NF compared to 2.45 in patients without (Bechar et al. 2017). Other studies have found a moderate positive predictive value and high negative predictive value of the score (Stevens and Bryant 2017).

Radiological investigations including radiographs, computerized tomography, and magnetic resonance imaging are helpful in the absence of classic findings such as crepitus. The presence of gas in the tissue warrants for immediate surgical exploration.

11.7 Treatment

Patients with NSTI and evidence of septic shock should be treated in intensive care units. As an intensivist, the primary goal of treatment, as with all cases of septic shock, is early antibiotic coverage, management of circulatory shock with fluid and vasopressors and early source control.

11.7.1 Surgical Intervention

Early and aggressive surgical intervention aimed at complete debridement is the mainstay of treatment. Delay in surgical intervention increases mortality (Freischlag et al. 1985; Hadeed et al. 2016) and the number of subsequent operations in survivors (Kobayashi et al. 2011). Surgical exploration helps in definitive diagnosis of NSTIs, sampling of tissues for gram stain and histology. Repeat explorations are often required for re-evaluation of wound and further debridement if required. In case of extensive tissue destruction, amputation, diversion colostomy, and reconstructive surgeries may be required.

11.7.2 Antibiotic Therapy

Early empirical antibiotic therapy should be broad spectrum with coverage of MRSA, gram negative bacilli, and anaerobes. Antibiotic therapy should be guided by local antibiogram. Empiric antifungal is not warranted. The current guideline published by the Infectious Diseases Society of America (IDSA) recommends vancomycin or linezolid, plus carbapenem/piperacillin-tazobactam/combination of ceftriaxone and metronidazole (Stevens et al. 2014). Specific therapy should be instituted after isolation of causative organisms based on susceptibility.

11.7.3 Adjuvant Therapy

Intravenous immunoglobulin (IVIG) has been advocated as a treatment of toxic shock syndrome due to streptococcal or staphylococcal NSTIs but the evidence behind its use is lacking. A randomized placebo controlled single center study on 100 patients found no benefit with IVIG adjuvant therapy on survival or self-reported physical functioning at 6 months (Madsen et al. 2017). Hyperbaric oxygen therapy has been proposed as an adjuvant therapy without any compelling evidence

(Bonne and Kadri 2017). AB103, a CD-28 receptor inhibitor, blocks the T-cell mediated response to streptococcal exotoxin and attenuates toxemia in mice infected with *S. pyogenes (*Ramachandran et al. 2013*)*. However, a randomized, placebo controlled trial involving 40 patients did not demonstrate any significant impact on resolution of organ dysfunction, number of debridement or cytokine levels (Bulger et al. 2014).

11.7.3.1 Surgical Site Infections

SSIs are the second most common adverse event seen in hospitalized patients (Leape et al. 1991). The occurrence of SSI depends upon the interaction of various risk factors including nature and site of surgery, technique involved, patient risk factors, etc. Surgical risk factors include site of surgery, nature of surgical wound, duration of surgery, prophylactic antibiotic omission, preoperative hair removal strategy, etc. Patient risk factors are advanced age, obesity, infections at other sites, ASA category, prolonged preoperative stay, malnutrition, immunosuppression, diabetes mellitus, and hypoalbuminemia (The Society for Hospital Epidemiology of America; The Association for Practitioners in Infection Control; The Centers for Disease Control; The Surgical Infection Society 1992).

SSIs are classified as superficial incisional, deep incisional, and organ space SSIs (Horan et al. 1992). Local signs of pain, redness, pus discharge reliably indicate an SSI. Fever is a non-specific symptom, more so in the first 48 h. Any suspicion of SSI should prompt an examination of surgical site. The cornerstone of therapy is suture removal, evacuation of infected collections and local wound care with regular dressing changes. Antibiotics are warranted only in the presence of features of SIRS or extension of erythema beyond 5 cm of incision line (Stevens et al. 2014). The choice of antibiotics should be based on the site of infection, the hospital antibiogram, and microbiological study. In general, clean surgical procedures that do not involve opening of gastrointestinal or genitourinary tracts, the wound infection is usually caused by *Staphylococcus aureus* from skin flora. SSIs following gastrointestinal or genitourinary procedures may involve Gram positive, Gram negative, and anaerobic organisms (Sartelli et al. 2014). The management of SSI is outlined in the recent guidelines (Stevens et al. 2014).

11.7.3.2 Infection of Bite Wounds

Animal and human bite wounds may get infected by oral flora and may lead to complications including osteomyelitis and septic arthritis. Along with rabies and tetanus prophylaxis, wound care for prevention of infection is an important aspect of management. Copious irrigation of bite wound and debridement of necrotic tissue should be done. Prophylactic antibiotics is of proven benefit in human bite wounds (Zubowicz and Gravier 1991) and should be considered in other bite wounds with high risk of infection such as bites on face, hands or feet, puncture wound penetrating the periosteum or joint capsule, or in patients with compromised immunity (Stevens et al. 2014). Infections are usually polymicrobial with mixed aerobes and anaerobes. In most cases, amoxicillin-clavulanate is an appropriate choice. In penicillin allergy, TMP-SMX for dog and cat bite wounds, and fluoroquinolones in

human bite wounds can be administered with additional anaerobic coverage with metronidazole or clindamycin (Stevens et al. 2014).

11.7.3.3 Infection of Pressure Ulcer

Pressure ulcers are localized areas of tissue necrosis that develops due to compression of soft tissue between a bony prominence and an external surface for a prolonged period of time (Garibaldi et al. 1981). Pressure ulcers develop by the interaction of intrinsic and extrinsic risk factors. Limited mobility and poor nutrition are the strongest intrinsic risk factors for pressure ulcer formation. Other important risk factors are increased age, chronic disorders (e.g., diabetes mellitus, cardiovascular disease, and stroke), anemia, increased blood urea nitrogen and serum creatinine, white race, skin abnormalities, and male sex (Keller et al. 2002; Livesley and Chow 2002). The most important extrinsic factor is pressure, but friction, shear stress, and moisture also play important roles in the development of pressure ulcer (Livesley and Chow 2002).

Infections of pressure ulcers are usually polymicrobial including *staphylococci* (including MRSA), *enterococci*, *Proteus mirabilis, E. coli, Pseudomonas* spp and anaerobic *Peptostreptococcus*, *Bacteroides fragilis*, and *Clostridium* spp. Pressure ulcers are a major reservoir of MRSA. A superficial culture cannot distinguish between colonizing and infecting organisms and a deep-tissue biopsy is required for accurate bacterial culture.

Prevention of decubitus ulcers is the best treatment. Pressure ulcers with local infection can be treated with debridement, application of moist occlusive dressing and application of topical antiseptic agents. Nutritional support and pressure relief by regular repositioning and using air mattress should be done. Topical agents used commonly are silver sulfadiazine, povidone-iodine, hydrogen peroxide, chlorhexidine gluconate. Topical antibiotics are not recommended (National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance 2014). In the presence of cellulitis and features of bacteremia, systemic broad spectrum empiric antibiotics should be administered. In case of failure of these lesions to heal, osteomyelitis should be ruled out by physical examination and imaging. Deep tissue biopsy and bone biopsy may be required in cases of nonresolution of infection for histopathology and culture and an extended course of systemic antibiotic therapy may be required in case of osteomyelitis (Evans and Steinberg 2017).

11.7.3.4 SSTIs in Immunocompromised Host

SSTIs in immunocompromised hosts present with unique challenges in the diagnosis and management. SSTIs in immunocompromised patients can be caused by unusual microorganisms and may be more difficult to eradicate with antibiotics alone (Sartelli et al. 2014). Additionally, fungal SSTI infections are more common in immunocompromised patients. Immunocompromised patients with NSTIs are associated with lack of typical clinical signs and consequent delays in diagnosis, leading to higher in-hospital mortality (Keung et al. 2013). Therefore, a thorough cutaneous examination of immunocompromised patients is important. The diagnosis of SSTIs needs to be confirmed against a broad differential diagnosis including

drug eruption, malignant infiltration and metastases, chemotherapy- or radiation-induced skin reactions, graft-vs-host disease among stem cell transplant recipients, leukocytoclastic vasculitis, and infections of fungal, mycobacterial, and parasitic etiology (Stevens et al. 2014). The diagnostic workup should, therefore, include an early biopsy or aspiration of sample for histological and microbiological investigations. Empiric antibiotics should be started on the basis of the type of immune defect, previous antimicrobial use, and local antimicrobial resistance profiles. Immunosuppressed status poses a high risk of development of resistance to empiric antibiotics and an early identification of pathogen should be attempted while evaluating the patient for an early surgical debridement (Stevens et al. 2014).

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Infections in Renal Transplant Recipient in ICU: An Overview

12

Praveen Tirlangi, Harsh Vardhan, and Manish Soneja

12.1 Introduction

Renal transplant has significantly improved quality of life and has shown to decrease mortality in patients with end-stage renal disease (ESRD) when compared to hemodialysis (Buzgova and Smotkova 2013). With the advent of newer immunosuppressants like calcineurin inhibitors, renal graft life has significantly prolonged but it comes with increased risk of infections. Adequate immunosuppression to prevent graft rejection is important but over immunosuppression should be avoided to prevent infections. Tilt in this fine balance to either side can result in adverse outcomes in the form of rejection or infectious complications. Infections are second most common cause of death with functioning graft after cardiovascular deaths in post-transplant recipients (Awan et al. 2018), though the literature is mainly from the western world. ICU admissions rates in post-transplant patients have decreased in the last two decades (Mouloudi et al. 2012; Sadaghdar et al. 1995). However; several biases like varying ICU admission policies across centers, ICU admissions as a bridge in immediate post-transplant period, and change in supportive care practices over period hamper any precise evaluation of the actual incidence of life-threatening complications leading to ICU admission. We will discuss the basics of transplant immunology, common infections in transplant patients, and challenges in the management of transplant patients admitted in ICU.

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12.2 Immunology

After an initial induction (ATG or Basiliximab) combination of oral immunosuppressants (Calcineurin inhibitors, mTOR inhibitors, anti-metabolites, and steroids) are used to prevent graft rejection. This net state of immunosuppression can predispose to infections which could be severe, atypical compared to the general population. Clinical assessment of the net state of immunity is the key to manage critically ill transplant recipients. Factors including the age, co morbidities, duration since transplant, drugs used in induction and maintenance regime, episodes of rejection where the immunosuppressant dose is escalated, history of opportunistic infections helps in assessing the immunological status of the patient. A biphasic immune response in sepsis with initial hyperinflammatory and subsequent state of immunoparalysis pose challenges in the assessment of immunological status. Post-transplant recipients with sepsis might not follow a classic biphasic immune response and may be immunoparalysed at the onset of sepsis. In such patients reduction in immunosuppression can increase the risk of rejection whereas, over immunosuppression can worsen the infection. Till now there is no biological marker available to objectively assess the immune status of the patient. Treating clinicians has to decide on immunosupression on case to case basis considering the risk of rejection and chances of opportunistic infections.

12.3 Infections

Despite improvements in both long term and short come outcome after renal transplantation infection remains an important issue and is one of the leading causes of ICU admissions. It is the second most common cause of death with a functioning graft after cardiovascular disease. Infections in the post-transplant period may follow a pattern related to timing after transplant (Fig. 12.1) (Fishman 2007). Infections can be donor-derived or could be due to reactivation or new infection in the transplant recipient. Donor-derived infections (DDI) account for 0.2%–1% of the total infectious disease burden in patients with all types of allograft recipients. DDI can be bacterial, fungal that occur during organ procurement or latent DDI like cytomegalovirus (CMV) or Ebstein-Barr virus (EBV) infection or latent tuberculosis (Jamal et al. 2014; Morton et al. 2014; Subramanian et al. 2013). Donor-derived infections, surgical site infections, and hospital-acquired infections predominate in the early post-transplant period (within the first month), whereas opportunistic infections due to immunosuppression are more common after one month. It is important to note that although this timeline of infections is a helpful starting point, the pattern and timing of infections may be significantly altered by the choice of immunosuppressive agents, net state of immunosuppression at different time points due to repeated acute rejections, as well as the choice and duration of antimicrobial prophylactic agents.

The predominant infections requiring ICU admission are described below.

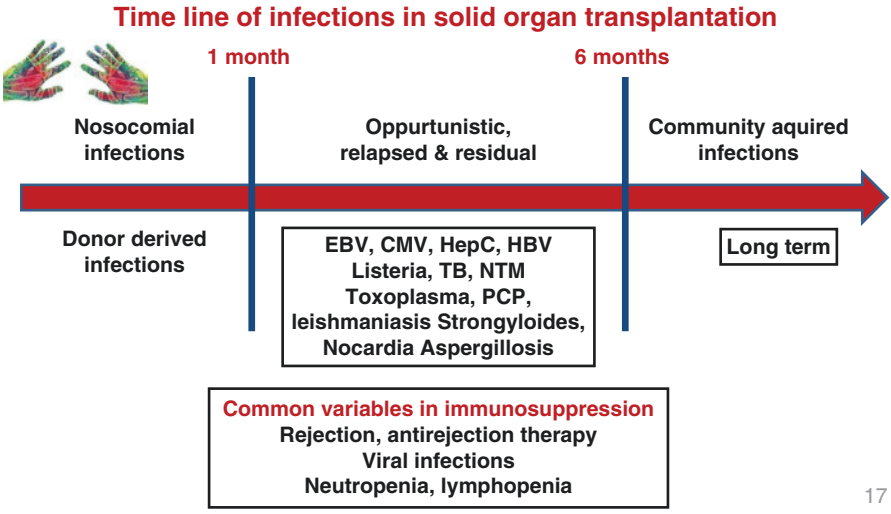

Fig. 12.1 Timeline of common infections in transplant recipients. *CMV* cytomegalovirus, *EBV* Epstein–Barr virus, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *PCP* Pneumocystis jiroveci pneumonia

12.4 Pulmonary Infections

Patients who are hospitalized in the immediate post-transplant period are at increased risk of hospital-acquired pneumonia due to MDR organisms whereas community-acquired pneumonia with typical and atypical organisms is more common later in the course. A high index of suspicion is required in diagnosing infections like pulmonary aspergillosis, mucormycosis, nocardiosis (Hamdi et al. 2014) as delay in diagnosis and treatment can lead to adverse outcomes. PCP associated pneumonia is one of the common opportunistic infections in renal transplant recipients requiring ICU admission. In half of the cases, it can lead to severe respiratory failure and if left untreated it causes mortality in around 30% (Roux et al. 2014; Canet et al. 2011). Though the role of steroids is well established in severe PCP associated with HIV, it is not well studied in the transplant recipient population. CMV-associated pneumonia was more common previously but with pre-emptive and better treatment strategies the incidence has declined (Jamal et al. 2014). Besides direct cytopathic effects, immunosuppressive mechanisms and cytopenias due to CMV increases the risk of other opportunistic infections (Howard and Najarian 1974). Recent observation suggests the increasing role of influenza virus infections in severe pneumonia associated with significant morbidity and mortality (Kumar et al. 2010). While clinical, radiological, and biomarkers help in presumptive diagnosis, definite diagnosis requires microbiological confirmation in sputum, BAL, or lung biopsy samples (microscopy, culture). Depending upon the clinical and radiological features, presumptive treatment should be started awaiting microbiological diagnosis.

12.5 Urinary Tract Infection

Urinary tract infections are the most common infection following renal transplant. It accounts for 50-75% of post-transplant infections and 30% of ICU admissions (Parasuraman et al. 2013; Lorenz and Cosio 2010). Female sex, deceased-donor transplant, kidney-pancreas transplantation with bladder drainage, prolonged catheterization, ureterovesical stents are associated with increased risk of urinary tract infections (Lorenz and Cosio 2010). Gram-negative bacteria of Enterobacteriaceae family, Pseudomonas, and Enterobacter species are the common causative organisms (Parasuraman et al. 2013).UTIs in kidney transplant recipients are considered complicated and thus standard treatment typically involves 7–14 days of antibiotic therapy; however, the optimal duration is not well defined. Other less common causes of UTI are fungal mainly Candida species.

12.6 Gastrointestinal Infections

Bacteria (E. coli, C. difficile, Shigella, Salmonella, and Yersinia), viruses (CMV, Rotavirus, Norovirus), parasites (Cryptosporidiosis, Cystoisospora, Cyclospora, microsporidiosis, Strongyloides) can cause diarrhea in post-renal transplant patients. Besides infections, drugs like mycophenolate mofetil, tacrolimus, cyclosporine, metformin, and post-transplant lympho proliferative disorder (PTLD) can also cause diarrhea (Helderman and Gora 2002). Diarrhea can be associated with transient increase in calcineurin inhibitor drug levels due to shedding of epithelial P-gp through which CNI is excreted into the gut lumen (Finch and Pillans 2014). In critically ill patients, Clostridium difficle infection, antibiotic-associated diarrhea, and food intolerance should also be considered in the differential diagnosis. Pseudomembranous colitis can be life-threatening for post-transplant patients (Neofytos et al. 2013).

12.7 Infections of the Central Nervous System (CNS)

CNS infections in post-renal transplant period can be fatal if not diagnosed and treated early. Fever, headache, meningismus, new-onset seizure, altered sensorium, or focal neurological deficits can be the presenting features. Besides infections, drug toxicity due to CNI can present with tremors, altered behavior, seizures, posterior reversible leukoencephalopathy (PRESS) and sometimes coma (Anghel et al. 2013). Differentiating drug toxicity from infections in critically ill patients is challenging. Furthermore, drug levels do not always correlate with toxicity. Bacterial and fungal infections can cause space-occupying lesions in the brain (Singh and Husain 2000). CNS lesions of aspergillosis mainly affect the temporal lobes at the grey and white matter junction and are multifocal. CNS lesions of candida are multiple, diffuse, small lesions, located both in the white and grey matter. Cryptococcus usually present with a headache with or without seizures and decreased

consciousness (Baddley et al. 2013). Infection due to Nocardia species requires a high index of suspicion even with patients on co-trimoxazole prophylaxis as resistance is common. Toxoplasmosis can also involve CNS mainly during the first post-transplantation trimester (Fishman 2007). Herpesviruses especially HHV-6 can present with disorders of consciousness due to meningitis and meningoencephalitis. Besides appropriate pharmacological treatment for causative organism supportive management for seizures and raised intracranial tension is important. Repeated lumbar puncture (cryptococcal meningitis) (Rolfes et al. 2014), pharmacological treatment (mannitol, diuretics, and steroids), extra ventricular drainage, and Omaya shunt (hydrocephalus) can be used in the management of raised intracranial tension. Drug interactions with antiepileptics should be considered when used along with calcineurin inhibitors and antifungal agents.

12.8 Bloodstream Infection

Renal transplant recipients are frequently admitted for sepsis with complications in ICU and some of them develop severe bloodstream infections (BSI) (Bige et al. 2014). Urinary tract infections with vesicoureteral reflux and catheter line-associated bloodstream infections are the common source. Infections with multidrug-resistant gram-negative organisms, MRSA, VRE requires removal of the catheter and antibiotic therapy. Aseptic precautions during insertion and handling of catheters, keeping the catheter hubs clean, daily examination of catheter exit site for redness and discharge are important in preventing and early recognition of catheter site infections. Gram-negative BSI, shock, and requirement of mechanical ventilation are independent risk factors for mortality (Silva et al. 2010).

12.9 Challenges in Management of Renal Transplant Patients in ICU

Management of any critically ill patient is challenging due to increased prevalence of MDR infections, altered PK/PD of drugs due to malnourishment, and organ failures. All these factors increase the risk of underdosing and increased drug toxicities. Post renal transplant status complicates it further due to drug interactions (mainly with CNI) and difficulty in differentiating side effects of drugs from atypical manifestations of infections. Calcineurin inhibitors can interact with a variety of commonly used drugs (azoles, calcium channel blockers, antiepileptics, antipsychotics, quinolone, and macrolide antibiotics) as they are substrates for cytochrome enzymes. The nephrotoxicity, neurotoxicity (psychosis, seizures, PRESS, and coma) of calcineurin inhibitors are difficult to distinguish from worsening of sepsis or other metabolic complications in critically ill patients. Renal injury due to CNI limits the use of nephrotoxic drugs commonly used in ICU (polymyxins, aminoglycosides, amphotericin B). Cytopenias caused by infections are difficult to distinguish from

Important drug interaction in managing infections in post-renal transplant recipient

	Treatment	Important drug interactions
Bacterial infections	Intravenous antibiotics depending on sensitivity patterns	Linezolid + MMF → cytopenias Cotrimoxozole + MMF → cytopenias Cotrimoxozole + CNI → risk of hyperkalemia Amikacin + CNI → nephrotoxicity Valganciclovir + imipenem → increased risk of seizures Polymyxins + CNI → nephrotoxicity
CMV	Ganciclovir/valganciclovir Foscarnet Cidofovir	Valganciclovir + MMF → cytopenias Valganciclovir + imipenem → increased risk of seizures
PCP pneumonia	? Steroids Cotrimoxazole Primaquine + clindamycin Dapsone	Cotrimoxozole + MMF → cytopenias
Nocardia	Cotrimoxazole Imipenem Amikacin Linezolid Doxycyclin	Valganciclovir + imipenem → increased risk of seizures Linezolid + MMF → cytopenias Cotrimoxozole + MMF → cytopenias Cotrimoxozole + CNI → risk of hyperkalemia Amikacin + CNI → nephrotoxicity
Aspergillus sps	Voriconazole Liposomal amphotericin B	Voriconazole decreases the metabolism of CNI → CNI toxicity Liposomal amphotericin B + CNI → increased nephrotoxicity
Mucormycosis	Liposomal amphotericin B Posoaconazole	Posaconazole decreases the metabolism of CNI → CNI toxicity Liposomal amphotericin B + CNI → increased nephrotoxicity

that of MMF in critically ill patients. The use of co-trimoxazole (PCP pneumonia, Nocardia, and toxoplasmosis) and ganciclovir (CMV infections) can be limited by the cytopenias caused by MMF. Diarrhea can decrease the absorption of MMF but it can also increase the blood levels of MPA due to decrease enterohepatic circulation. This makes the serum drug levels unpredictable and subsequently increasing the risk of both rejection and hematological toxicities. MMF absorption can be decreased due to substances containing divalent cations (multivitamins, calcium-containing phosphate binders). Routinely used drugs in the management of atrial fibrillation, epilepsy, delirium can have significant interactions with immunosuppressants and antimicrobial agents. If neglected, these interactions can result in therapeutic failure, rejection and drug toxicities (see Table 12.1).

12.10 Summary

Renal transplantation is the treatment of choice for ESRD patients. Better immunosuppression has improved graft survival and function, but they contribute significantly to post transplantation complications which include major cardiovascular events, malignancies and infections. Cardiovascular causes and infections are the major cause of ICU

Table 12.1 Outline of management of atypical infections in renal transplant recipient

Organisms	Management
CMV	• Inj. ganciclovir 3–5 mg/kg body weight intravenous 12th hourly • Can be converted into equivalent doses of Oral Valganciclovir if absorption is good • Monitor CMV viral load (less than 1 log reduction in 2 weeks is failure) • Consider reducing immunosuppression
Norovirus	• Supportive management • Tab nitazoxanide and IVIG can be considered (Off label use)
Nocardia	• Induction: 3–6 weeks followed by maintenance for 12 months • Combination treatment according to drug sensitivity • Effective drugs: co-trimoxazole, amikacin, imipenem, meropenem, linezolid, minocyclin, levofloxacin, ceftriaxone
Aspergillus spc	• Inj. voriconazole 6 mg/kg intravenous 12th hourly followed by 4 mg/kg i.v or oral 12th hourly • Oral voriconazole to be taken empty stomach • Monitor drug levels • Consider reducing immunosuppression
Mucormycosis	• Inj. liposomal amphotericin B 5 mg/kg intravenously for 4–6 weeks f/b • Tab posoconazole 200 mg QID (with fatty food or cola drink) • Monitor drug levels • Consider reducing immunosuppression
Pneumocystis jiroveci	• Tab. co-trimoxazole (15–20 mg/kg trimethoprim equivalent) for 21 days Steroids
Cryptococcal meningitis	• Inj. liposomal amphotericin B 3–5 mg/kg intravenous + Tab Flu cytosine (100 mg/kg body weight) for 2 weeks • f/b Tab fluconazole 400 mg OD for 2 months f/b OD • Monitor drug levels
Strongyloides	• Tab ivermectin 200 ug/kg, maximum of 12 mg single dose • For hyper infection treatment should be continued till symptoms resolve and stool examination is negative for at least 2 weeks
Toxoplasmosis	• Tab pyrimethamine + sulphadiazine is drug of choice • If not available Tab co-trimoxozole (800/160) 2 tab BD can be used for 6 weeks

admissions and mortality is transplant patients. A high index of suspicion with early recognition of the signs and symptoms and early initiation of treatment for infections can be life saving. Optimization of immunosuppressant's, drug interactions, drug toxicities and altered pharmacokinetic and pharmacodynamic properties of drugs are major challenges in managing critically ill patients. A holistic approach with clinical assessment of immunological status, high index of suspicion for atypical infections and atypical manifestations of common infections, early diagnosis and treatment are key aspects in the management of renal transplant recipient in intensive care units.

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Infections in Burn Patients in ICU

13

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13.1 Introduction

Critically ill burn patients usually carry a higher risk of infections. Infections and subsequent complications are the leading cause of death in burns after initial couple of days where the main causes are Hypovolemia and Hypoxia (in Inhalational Burns). Although advancements in burn management and critical care have decreased the mortality rate in severe burn injuries, infections continue to be a challenge. Management of burn patients in the ICU involves management of physiological derangements caused by burns, management of various catheters and tubes used for invasive monitoring, optimum nutrition along with local wound care.

13.2 Epidemiology

Infection is the most important cause of death among burn patients. In present times pneumonia is the most common infection in patients with burns, burn wound infection still remains a severe complication unique to the burn victim. Burn wound management has evolved over the past 50 years. This evolution goes hand in hand with the epidemiology of burn associated infections. Between 1950s to 1980s, burn wounds were treated with topical antimicrobials and gradual debridement with immersion hydrotherapy. Since then there was a shift in the management to early excision and wound closure (by skin grafting or primary closure) which has hastened wound healing and apparently reduced overall burn wound infections. There is limited data on the epidemiology of burn wound infections since this paradigm shift (Weinstein and Mayhall 2003).

In a prospective study, 90 infections (34%) of 116 burn patients over 1 year (de La Cal et al. 2001). The most common infections were pneumonia and burn wound infection, and S. aureus was identified as the causative microorganism in 37% of the cases.

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More recently, a study on the incidence of infections in burn patients was performed in a Swedish University Hospital from 1993 to 1995 (Hidalgo et al. 2016). Of the 230 burn patients, 83 (36%) developed 176 infections. Infection of the burn wound was the commonest (107 infections in 72 patients). Fourteen patients developed 17 episodes of pneumonia at a median of 3 days post admission. Of the 17 pneumonia episodes, 13 were bacterial and were predominantly caused by S. pneumoniae (6 cases) and S. aureus (3 cases).

13.3 Microbial Aetiology

The flora colonizing and infecting critically ill burn patients without comorbid illnesses or infections follows a characteristic pattern:

1. On admission patients without pre-existing illnesses, potentially pathogenic microorganisms (PPM) carried in digestive tract and skin are similar to those usually borne by healthy subjects.
2. Later that flora is replaced by the catheter-related (acquired) flora. The digestive tract of other patients acts as an important reservoir.
3. Ninety-nine percent of infections in severely burnt patients are caused by PPM previously. Isolated in the gastrointestinal tract of the patient. They are considered endogenous (Ramos et al. 2002) (Fig. 13.1).

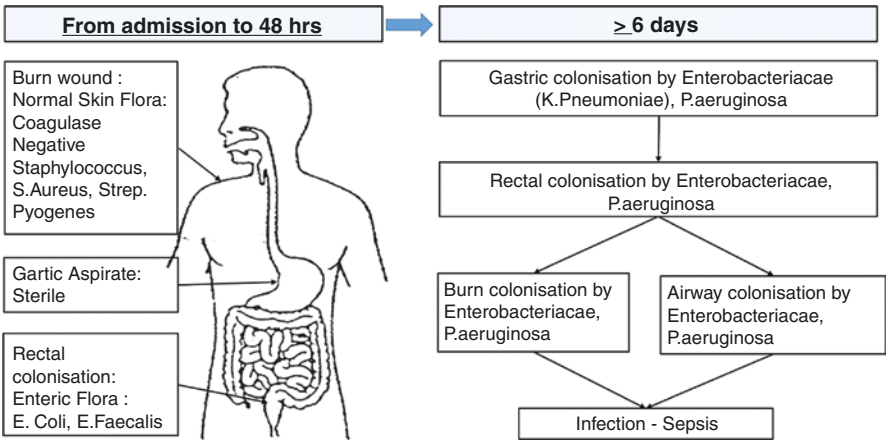

Fig. 13.1 The chronology of burn colonization and infection in ICU. Modified Hidalgo et al. (American Burn Association 2019)

Causative agents of infection in burns include

- *Bacteria*: *Gram-positive bacteria*—Streptococcus pyogenes and Staphylococci, especially methicillin-resistant Staphylococcus aureus (MRSA) cause catheter colonizations and subsequent blood stream infections.
- *Gram-negative bacteria*—Such as Pseudomonas aeruginosa (most frequently found in burn wounds), Klebsiella species, E. coli, Acinetobacter baumanii, Proteus species (Pruitt Jr 1980).
- Pseudomonas infection can present with a dark purple, blue lesion in the non-burnt skin this is known as ecthyma gangrenosum. It is characterized by perivascular haemorrhage and thrombosis. A multidrug-resistant form of pseudomonas has emerged, making treatment even more difficult.
- *Fungi*—Candida is usually the most common fungal isolate, but has a low potential for invasion. Candida colonization is as high as 30% in cases with more than 40% surface area involved. Candida is usually filtered out of the blood at the capillary level; arterial blood cultures are recommended. In the case of fungal sepsis, they can be isolated from urine also.
- On the other hand, Filamentous fungi, such as Aspergillus, Fusarium, and Phycomycetes, can be aggressive invaders of subcutaneous tissues in severe burns receiving prolonged antibiotic treatment. Histologically, the presence of fungal hyphae extending like fingers between necrotic and intact dermis are diagnostic of invasive fungal infections. Removal of all dead tissue, systemic antifungals like voriconazole, posaconazole etc. has been used successfully in treatments.
- *Viruses*—such as herpes simplex.

The various routes by which the organisms can enter the body (Weinstein and Mayhall 2003) are:

- *Burn wound*: The patient's flora residing in the dermal elements is the first to infect the wound. Subsequently, exogenous organisms may also invade.
- *Respiratory*: Infection of the lower respiratory tract is common in patients with inhalational injury. It is a significant cause of death from sepsis.
- *Intravenous catheters*: The veins in and around the burn wound is likely to be a source of invasive infection. Ramos et al. in a prospective observational study (Ramos et al. 2002) reported a cumulative incidence of bloodstream infection in 20 patients. They observed that if a catheter insertion site was within an area of 25 cm^2 around burn wound, the incidence of bloodstream infection was 27%, but at a greater distance, it was 6%. Thus it is advisable to keep the site of catheter insertion away from burn wounds.
- *Urinary tract*: Prolonged catheterization is a source of UTI. This may be required to prevent soiling of dressings in perineal burns.
- *Gastrointestinal tract*: Translocation of bacteria from the gut following vasoconstriction and mucosal erosions is an essential cause of sepsis in burns. This emphasizes the importance of maintaining normovolaemia and eneteral nutrition in critical patients.
- *Miscellaneous*: Escharotomy incisions, burned areas which involve the cartilage, e.g. the burns of the pinna, are particularly susceptible to infection. Suppurative chondritis, endocarditis, arthritis can also cause sepsis in patients.

13.4 Pathophysiology

Burn wounds are *initially sterile.* The heat that burns the skin also kills the microorganisms in and around the burn wound. However, patients with extensive burns are immunocompromised and more prone to infection than healthy individuals on antibiotics (Weinstein and Mayhall 2003).

Critically ill burn patients are more vulnerable than other critically ill patients to acquire infections. Increased propensity can be attributed to the following factors:

1. Loss of skin protection(first line of defence against microbial invasion), in some cases respiratory injury from smoke inhalation.
2. A generalized immunosuppressive state induced by extreme stress i.e. burns.
3. Frequent use of invasive devices for diagnostic and therapeutic purposes (tracheal intubation, prolonged intravascular catheters, urinary catheters).
4. Surgery carried out in areas with flora colonizing burn wounds is associated with transient bloodstream infection.
5. Presence of devitalized, avascular tissue provides a favourable environment for microbial growth.
6. The erosion of the stomach lining and duodenum leading to gastrointestinal translocation.

13.5 Burns Assocoiated Infections

13.5.1 Pneumonia

According to the American Burn Association, National Burn Repository 2019 Pneumonia was one of the most frequent occurring complication accounting for 4.1% of fire/flame-injured patients. The incidence of pneumonia and septicemia was higher in patients with four days or greater of ventilator stay (American Burn Association 2019). Ventilator-associated pneumonia in burn patients is three times higher than in other patients in the ICU.

The causes of infection can be aspirated bacteria (better prognosis), direct contamination of tracheobronchial tree or haematogenous spread from burn wound.

In a prospective study by Miguel de la Cal et al. (Ramos et al. 2002) 95% of the episodes of pneumonia were caused by microorganisms that were previously colonized the digestive tract viz. S. aureus

Streptococcus pneumoniae and Haemophilus influenzae. Later appearing pneumonia was exogenously acquired in the ICU.

13.5.2 Urinary Tract Infections

Indwelling urinafry catheter is required for monitoring urine output in burn patients; this can be a source of infection as it is usually kept for an extended period. Samples

for culture should be sent thrice a week, and unnecessary use of catheter should be avoided.

Urosepsis is not a significant factor for sepsis in this subset of patients. Culture should be inquired if a burn patient has fever and sepsis with no other identifiable source.

A somewhat challenging problem is candiduria. Sometimes, changing the urinary catheter is sufficient to mitigate the source of sepsis. Occasionally, antimicrobial treatment needs to be initiated.

13.6 Central Venous Access Related Infections

The US Centres for Disease Control and Prevention (CDC) subdivision on Nosocomial Infection Surveillance System observed that out of all ICUs, burn ICUs have the highest incidence of primary central line related blood stream infections. This indicates use of a central line only when necessary in a burn patient. A peripheral catheter through unburnt skin should be preferred route of venous access. A central catheter should only be used to monitor initial resuscitation or for long-term parenteral nutrition.

The site of choice for venous access placement in the order of preference are:

1. Peripheral vein; unburnt area
2. Central vein; unburnt area
3. Peripheral vein; burnt area
4. Central vein; burnt area (worst choice)

Certain recommendations by the American society of Anaesthesiologists regarding practices related to central line placement are as follows (Practice Guidelines for Central Venous Access 2020):

1. Aseptic techniques such as hand washing, use of barrier precautions (e.g., sterile gowns, sterile gloves, caps, masks covering mouth and nose, and patient drapes) should be used.
2. Chlorhexidine or povidone-iodine containing solution should be used for access site preparation.
3. Catheters coated with antimicrobial agents are not a substitute for standard infection preventive strategies. However, can be used for selected patients based on anticipated duration of catheter use, cost and risk of infections.
4. After catheter insertion the site should be dressed with transparent chlorhexidine containing bio-occlusive dressing.
5. The need for keeping the catheter in situ should be assessed on a daily basis and should be removed promptly when it is no longer needed.
6. The site of catheter insertion should be inspected daily to watch for any signs of infection, at any suspicion of infection, the catheter should be removed immediately and if reinsertion is needed, it should be done through a fresh site.

13.6.1 Blood Stream Infections

Intravascular lines can be a major source of infection in burn patients. There have not been many clinical trials regarding prevention of catheter-related sepsis in burn patients; it is generally recommended to change intravascular catheters every 5–7 days in patients with burns involving ≥20% TBSA (total body surface area) requiring intravascular fluids/medications. Also, wherever possible, the catheter should be placed away from burn or surgical wound.

Diagnosis is made if the patient has a recognized pathogen or skin contaminant cultured from two or more blood cultures, or one positive blood culture, in the presence of clinical sepsis (Greenhalgh et al. 2007).

In patients with burns, most common infecting organisms are gram-negative bacilli and Staph. Aureus, thus in suspected bloodstream infection empirical antibiotics targeting these organisms should be started.

13.7 Burn Wound Infection

13.7.1 Important Definitions

Colonization The presence of bacteria less than 10^5 organisms per gram of tissue without any signs of inflammation is termed as colonization. These bacteria are present on the burnt tissue superficial to the eschar.

Non-Invasive Wound Infection The bacteria that colonized the wound now penetrate the eschar and aid in its separation. The count rises more than the critical level of 10^5 organisms per gram tissue with signs of local inflammation.

Invasive Burn Wound Infection When bacterial counts exceeds 10^5 organisms per gram of tissue, it is at risk for developing invasive burn wound infections, even when the wounds are excised. Although the ability of burn wound excision to decrease bacterial counts, burn wounds with high counts are at risk of developing burn wound sepsis due to involvement of non burnt area because of the bacteremia, both before and after surgery (Barret and Herndon 2003).

For the purpose of surveillance a committee under American burn association (Peck et al. 1998) suggested the following definitions for burn wound infections:

Burn wound impetigo	The loss of epithelium in previously re-epithelialized areas such as grafts, donor sites and secondarily healed wounds. It may or may not be associated with Inflammatory systemic symptoms
Open burn-related surgical wound	It is characterized by the presence of culture-positive purulent exudate and may often be associated with loss of skin grafts (biological and/or artificial dermal substitutes)

Burn wound cellulitis	The presence of erythema along with other signs of inflammation such as calor, dolor, oedema and lymphangitis beyond the area of the wound is the hallmark in such cases
Invasive infection in unexcised burn wounds	Unusual discolouration of unexcised eschar along with local and systemic signs of infection is characteristic
Other unusual infections exclusive to deep burns are *fasciitis and myositis*	

13.7.2 Chondritis

It usually occurs 3–5 weeks after the burn injury. It can be seen in both partial- and full-thickness injuries involving the auricle, though it is more common in the latter. Since the ear cartilage is a single piece of elastic cartilage, even a small area of exposed/infected cartilage has the potential for infection of the entire ear cartilage. The ear initially becomes inflamed and oedematous; the condition is painful. Treatment involves incision and drainage of the ear and removal of purulent and necrotic tissue; this is done by giving an incision at the helical margin. Along with the procedure and local wound care, the appropriate antibiotic is given.

13.7.3 Ophthalmic Infections

Problems such as loss of corneal epithelium, lid retraction can cause permanent damage to the eyes. It is therefore vital to prevent such complications with frequent instillations of antimicrobials eye drops, interventions like lid taping, tarsorraphy and sometimes an early release of lid ectropion and avoiding exposure to trauma.

13.8 Clinical Features

Local Signs: The presenting features are black or dark brown focal areas of discolouration; early separation of eschar, conversion of partial-thickness burns to full-thickness burns; spread of inflammation and oedema in surrounding skin adjacent to burn margin; increased friability and bleeding from granulation tissue; eruptions of papules and rashes in surrounding skin and elsewhere in the body (Sarabahi et al. 2010).

Besides the local signs, there may be systemic signs of infection, depending on whether the causative organism is gram positive or gram negative.

13.9 Signs of Gram-Negative Septicaemia

1. Symptom onset is rapid within 8–12 h along with fever (100–103 °F), tachycardia and tachypnea.
2. Presence of a bounding pulse.
3. Initially, there is normal or raised systolic blood pressure (high output shock).

4. Vasodilatation may decrease diastolic pressure to a considerably low limit, thereby varying the pulse pressure.
5. Subsequently, if sepsis continues, systolic pressure also decreases (low output shock)
6. Multiorgan dysfunction may ensue, causing renal failure, ARDS, DIC, diarrhoea, disorientation. Low platelet count may occur in initial stages as well.
7. The wound has the appearance of focal gangrene.

13.10 Signs of Gram-Positive Septicaemia

1. Symptoms gradually increase and are associated with high-grade fever (105 °F) and leucocytosis.
2. Fall in blood pressure, paralytic ileus and oliguria are usual in initial stages
3. The wound appears macerated with thick tenacious discharge.

13.11 Systemic Inflammatory Response and Sepsis

Extensive burns >20% TBSA incite a profound inflammatory response, thus going by the definition all burn patients have SIRS irrespective of infections.

The definition of sepsis for a non-burnt population is also less applicable to burn patients as (fever, tachycardia, tachypnea, leukocytosis) that are routinely found in patients with extensive burns. Thus the American Burn association held a consensus to define sepsis in burns with the following criteria (Table 13.1):

13.12 Investigations

13.12.1 Cultures and Histopathology

The clinical criteria for the diagnosis of burn wound infection are more critical in comparison to other battery of examinations. The treatment is guided by culture from wound exudates and blood.

The biopsy cultures of burn wound have minimal significance for the diagnosis of infection. The histopathologic examination in clinical practice should only be performed if there is suspicion of invasive fungal infection.

While samples for wound culture are being taken, the following measures should be followed: (Murray and Baron 2003).

1. An area of active infection and sufficient volumes of sample to obtain the specimen should be chosen for sampling.
2. As far as possible avoid contamination with the healthy flora, the container should be designed to promote survival of the suspected pathological agent (e.g. MacConkey agar or brain heart infusion agar culture media)

Table 13.1 Diagnostic criteria for sepsis in burn patients (Greenhalgh et al. 2007)

The trigger includes at least three of the following criteria:
1. Temperature >39 °C or <36.5 °C
2. Progressive tachycardia
(a). Adults >110 bpm
(b). Children >2 SD above age-specific norms (85% age-adjusted max heart rate)
3. Progressive tachypnea
(a). Adults >25 bpm in not mechanically ventilated
Minute ventilation >12.1/min in ventilated
(b). Children >2 SD above age-specific norms (85% age-adjusted max respiratory rate)
4. Thrombocytopenia (will not apply until 3 days after initial resuscitation)
(a). Adults <100,000/mcl
(b). Children < 2 SD below age-specific norms:
5. Hyperglycemia (in the absence of pre-existing diabetes mellitus)
(a). Untreated plasma glucose > 200 mg/dL or equivalent mM/L
(b). Insulin resistance—examples include
• >7 units of insulin/h intravenous drip (adults)
• Significant resistance to insulin (>25% increase in insulin requirements over 24 h)
6. Inability to continue enteral feedings >24 h
(a). Abdominal distension
(b). Enteral feeding intolerance (residual >150 mL/h in children or two times feeding rate in adults)
(c). Uncontrollable diarrhoea (>2500 mL/day for adults or >400 mL/day in children)
In addition, it is required that a documented infection (defined below) is identified:
(a). Culture-positive infection, or
(b). Pathologic tissue source identified, or
(c). Clinical response to antimicrobials

3. Properly labelled and preserved specimens must be promptly transported to the laboratory, preferably within 2 h.

Demonstration of $>10^5$ bacteria per gram tissue by quantitative assay (or recovery of mould or yeast by culture) is diagnostic of burn wound infection. Besides, the presence of microbial invasion into adjacent healthy tissue has been suggested as a specific criterion by the American Burn Association (ABA) to define burn wound sepsis.

13.12.2 Biomarkers

The use of biomarkers in burn patients can help to differentiate SIRS from infection for early initiation of systemic antibiotic therapy. This has been studied in a systematic review of 6 studies specific to burn patients by Mann et al. (Silvestri et al. 2007) The studies collectively demonstrated the benefit of incorporating procalcitonin determination in diagnosis of sepsis as procalcitonin levels greater than 2.5 ng/mL or 3 ng/mL favours the diagnosis of sepsis. Small sample size and inconsistent results limited the study. Also, dearth of rapid and cost-effective tests restrict the utility of procalcitonin assay in routine clinical practice.

13.12.3 Burn Unit Antibiogram

The pattern of antibiotic sensitivity of microbes in burn wound should be determined periodically. The susceptibility and resistance of microorganisms are noted at the burn centre. This would help in the use of empirical antibiotics which can be started when early signs of sepsis are present, and a positive culture is not available.

13.13 Management

13.13.1 Infection Prevention-Selective Digestive Decontamination

It is the single most crucial infection prevention strategy that has consistently demonstrated reduce mortality in critically ill populations (Liberati et al. 2009). Selective digestive decontamination (SDD) was initially formulated for the prevention of pneumonia due to ventilators in ICU, caused by aspiration but subsequently, it is effective in preventing gram-negative bacilli septicemia, due to translocation of bacteria through the gut wall (Silvestri et al. 2007). It acts by eradication carrier state of the PPM in oropharynx and GI tract (Taylor et al. 2007).

The protocol of the SDD includes Fig. 13.2:

The use of DDS has been evaluated in severe burn patients in a randomized controlled clinical trial (de La Cal et al. 2005), and one observational study (Mackie et al. 1992) and have shown significantly lower mortality and incidence of pneumonia in both the studies.

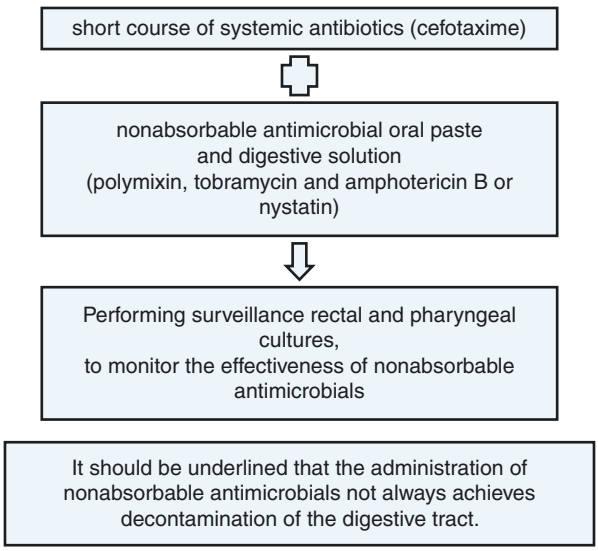

Fig. 13.2 Protocol for selective digestive decontamination

13.14 Treatment

Burn wound infection is treated by a combination of cleaning and debridement, topical or systemic antibiotic therapy and excision and wound closure techniques.

Deep burn wounds are currently managed by early excision and grafting between 1 and 7 days. This practice is based on two rationales.

1. the dead burnt tissue is prone to infection
2. it promotes the production of proinflammatory molecules associated with multi-organ failure.

The role of early excision has not been studied in critically ill burn patients, and topical application of antimicrobial allows to delay surgery in high-risk patients (hemodynamically unstable, multiorgan failure).

This practice helps to buy time and to individually set the timing and areas to be excised for each critical patient.

13.15 Topical Antibiotic

Various topical products are available with a spectrum of antimicrobial activity (Robson 1977).

Silver nitrate: It is bacteriostatic against Staphylococcus aureus, Pseudomonas aeruginosa, E. coli, it is used as 0.5% solution. It has limited eschar penetration. The disadvantages are that it turns the tissue black, there is also a risk of hyponatremia and hypochloremia.

Silver sulfadiazine: It is effective against P. aeruginosa, the enterics, as well as C. albicans and S. aureus. It acts by silver ion binding with the DNA of the organism, releasing the sulfonamide which disturbs the metabolic pathway of the microbe. It has poor eschar penetration. It is used as 1% cream that is effective for about 24 h.

Mafenide acetate: it is available as 8.5% water soluble cream or 5% solution. It is effective against a wide range of microbes. It has good eschar penetration. However, the application is painful, and there is a risk of metabolic acidosis. It needs to be applied 2–3 times daily.

Mupirocin: it acts by inhibition of microbial isoleucyl-tRNA synthetase that causes inhibition of protein synthesis in the bacterial cell. It is derived from P.fluorescens fermentation. It is effective against methicillin-resistant Staphylococcus aureus.

Povidone-iodine: it is known to be effective against a wide variety of fungal and bacterial agents. It is available as a ten percent ointment or solution. Six hourly application is recommended.

Silver dressings: recently, advanced silver impregnated dressings such as Acticoat (Smith & Nephew), Mepilex Ag (Mölnlycke), Biatain Ag (Coloplast) etc. have been introduced that carry the microbicidal capacity of silver and are absorbent as well. This allows less frequent change of dressings, better patient compliance along with controlling local wound infection.

13.16 Systemic Antibiotics

Use of prophylactic systemic antibiotics is not recommended. Systemic therapy becomes essential in cases where the burn wound sepsis is present. Usually, the standard regimen is to use a combination of a third-generation cephalosporin with sulbactam or use of piperacillin and tazobactam. These drugs are active against gram-positive organisms, considering it is usually patients own flora that is the cause of infection in most cases. Antifungals such as amphotericin or caspofungin should be used as per the culture sensitivity, keeping in mind the nephrotoxicity of these drugs. Wound and blood cultures should guide us for using the correct systemic therapy to achieve maximum benefit while causing the least resistance.

13.17 Operative Wound Management

Tangential excision and grafting are performed within 1–7 days post burn. It allows removal of dead tissue and immediate cover of the area with a split skin graft (autograft or allograft, both can be used depending upon the availability). In the later stage also debridement of the wound is necessary to get rid of the necrotic tissue so that the region becomes amenable to secondary grafting.

13.18 Nutrition

Adequate nutrition is the cornerstone of treatment in burn patients. Lack of proper nutrition can lead to delayed wound healing, weight loss and susceptibility to sepsis. Enteral feeding is encouraged, and in patients who are unable to take adequate amounts peroral or with the help of nasogastric/orogastric tube, parenteral nutrition is given. One of the formulae for determining the calorie requirement in burn patient is the *Curreri formula:*

Calories needed per day = 24 kcal × Kg (wt) + 40 kcal × % total body surface area (TBSA) burn (Using a maximum of 50% burn).

Diet should consist of about 20% fats, 60–70 % carbohydrates and usually double the standard requirement of proteins.

13.19 Recent Advances

13.19.1 Topical Burn Wound Management

Nowadays, an array of burn dressing materials is available which provide benefits of enhanced antibacterial activity, reduced frequency of dressing and more patient comfort (Important Developments in Burn Care 2019) (Table 13.2).

Silver sulfadiazine is a commonly used topical antimicrobial, but many pseudomonas species have been resistant to and poorer healing outcomes.

Newer silver dressings such as Acticoat contain sustained release silver ions which have extended antimicrobial spectrum including methicillin-resistant

Table 13.2 Newer burn wound dressings

Dressing type	Feature	Example
Hydrocolloid	Forms gel on contact with exudate	Comfeel, duoderm
Polyurethane	Permeable to water vapour and oxygen but not to liquid or bacteria	Opsite, tegaderm
Hydrogel	High fluid absorbing capacity	Intrasite, solugel
Silicone coated Nylon antimicrobial	Non adherent, exudate drainage, contains silver or iodine	Mepitel silicone, Acticoat, iodosorb, aquagel Ag
Biosynthetic skin substitutes	Support reepithelization	Biobrane, transcyte, integra
Foam	Easy to change, absorbent	Mepilex Ag

Staphylococcus aureus (Wasiak et al. 2013; Strand et al. 2010; Khundkar et al. 2010). They also reduce the pain and pruritus and frequency of dressing and thus increased patient compliance.

A Cochrane systematic review was conducted in 2014 to evaluate the safety and effectiveness of NPWT for partial-thickness burns. The study concluded dearth of enough evidence to permit any conclusions to be drawn regarding the use of NPWT in open burn wounds (Dumville et al. 2014).

13.20 Surgical Burn Management

Early tangential excision of deep burn wounds is a norm to promote rapid wound healing and prevent infection. The amount of blood loss associated with this is estimated at 190–270 mL/percent TBSA excised and continues to be a challenging aspect of the surgery (Wasiak et al. 2013). Newer haemostatic strategies include subcutaneous epinephrine infiltration, limb tourniquets, electrocautery, fibrin sealant and topical epinephrine or thrombin (Strand et al. 2010). Diligent use of a combination of these techniques can effectively reduce blood loss.

In burn patients, intraoperative hypothermia (<36.0 °C) has been shown to be associated with significantly increased blood loss (Khundkar et al. 2010; Dumville et al. 2014). It is also linked to acute lung injury (Martyn 1986) and increased incidence of wound infections in burn patients (Ortwine et al. 2015).

Various strategies that help in maintaining intraoperative normothermia are increasing the ambient room temperature, infusing warmed fluids and using forced-warm-air inflatable blanket technologies, such as the Bair Hugger (caution is needed as paradoxically this equipment may sometimes lead to accidental burn injury).

13.21 Further Reading

Hypermetabolic response—Its Effect on Drug Delivery and Metabolism:

Severe burn injury incites profound physiological changes in the body that alters antimicrobial pharmacokinetics and pharmacodynamics. These changes significantly impact drug distribution and excretion.

In the acute phase, due to hypovolaemia and hypoperfusion of tissues, intravenously administered drugs have a slower onset, a slower rate of distribution and elimination through kidneys. Due to hypoperfusion of skin, muscles and gut, burn patients also exhibit delayed absorption of drugs given through subcutaneous, intramuscular and enteral routes. Drug regimens during acute phase will cause delayed onset of action and peak plasma concentrations (Martyn 1986).

During the hypermetabolic phase, due to increased levels of catecholamines, cortisol and glucagon, there is increased blood flow to organs and tissues. This increases the rate of distribution, and thus, intravenous drugs have an increased onset of action. Due to increased renal blood flow and GFR, the renally excreted drugs are rapidly eliminated and have a shorter half-life. The drug requirement (dosage and frequency) of drug increases during the hypermetabolic phase. Oral medications will also exhibit an increased absorption from the GI tract and rapid onset of action.

During this phase, there is also reduced albumin levels and increased level of acute phase proteins. Albumin usually binds to acidic and neutral drugs such as aztreonam, cefotetan, aminoglycosides and vancomycin. Higher drug dosages may be necessary to produce a therapeutic effect.

In the liver phase I metabolism is reduced. This will affect the metabolism of many antibiotics, such as the quinolones and the macrolides. This may lead to a longer half-life and increased systemic toxicity. Phase II metabolism, such as conjugation reactions will not be impaired.

In a recent review by Ortwine et al. (2015), they have summarized the existing literature regarding the pharmacokinetics and pharmacodynamics of antibiotics and antifungal agents in the burn population and provided suggestions on dosing. It included commonly used antibiotics such as Beta-lactams, carbapenems, aminoglycosides, vancomycin, daptomycin, linezolid and colistin.

13.22 Conclusion

From the time the burn takes place to its final healing, prevention of infection plays a key role in its management. Not only is the wound itself is prone to contamination, but also measures taken for burns management such as intravenous lines and catheters can themselves because of life-threatening sepsis in the patients. Keeping in mind the occurence of numerous multidrug resistance organisms, judicious use of available antibiotics can help achieve efficient management of burn wounds. It is important to consider that in a patient with burns, efficient management of his or her nutritional status, other medical illnesses, pain-relief, ambulation, mental health, compliance, etc. are equally important besides the management of burn wound itself.

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Approach and Management of Severe Infections in Neutropenic Patients

14

Prantar Chakrabarti and Ankit Kumar Jitani

14.1 Introduction and Definition

Humanity has three great enemies: fever, famine, and war (Bryan 1996) and fever by far is the greatest and the most terrible of the three. Fever is the defining event of severe infection and defining fever has been a major challenge with different proposed thresholds. The mean oral temperature in health is 98.2 °F, with a range of 96 °F–100.8 °F and a slight diurnal variation (Mackowiak et al. 1992). Fever, as defined by the Society of Critical Care Medicine and the Infectious Disease Society of America, is an oral temperature of above 101 °F (O'Grady et al. 1998). Fever in a neutropenic patient has different defining thresholds. Febrile neutropenia is defined by a single oral temperature of 101 °F or a temperature of more than 100.4 °F sustained over a period of 1 h. Axillary temperature may not reflect core body temperature and rectal temperature measurement may result in colonizing of gut commensal into the surrounding mucosa, and hence both are discouraged (Freifeld et al. 2011). The defining temperature threshold at times rests at the intensivist's discretion and the clinical condition of the patient.

Risk of infections secondary to neutropenia begins to rise with an absolute neutrophil count (ANC) of <1000 cells/mm^3. Febrile neutropenia is defined as ANC <500 cells/mm^3 or an ANC which is expected to reduce to <500 cells/mm^3 over the next 48 hours, and this predisposes the host to severe life threatening infections. The term *profound neutropenia* is used when the ANC is <100 cells/mm^3 and *prolonged neutropenia* when the duration of neutropenia exceeds 7 days. *Functional neutropenia* is another term worth mentioning here in which there is normal ANC but there is impaired neutrophil functioning that increases the susceptibility to infection in the host (Freifeld et al. 2011).

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14.2 Epidemiology

The incidence of neutropenic sepsis reported in literature lacks uniformity in criteria used to define febrile neutropenia. A patient with solid tumor has around 10–40% risk of developing febrile neutropenia, whereas the risk may be as high as 80% in hematological malignancies (Flowers et al. 2013; Aarts et al. 2013). The incidence of catheter related bacterial infection in neutropenic subject ranges from 16.2 to 24.3/1000 neutropenic days, depending upon the quality of line handling (Chaberny et al. 2009). Risk of blood stream infections secondary to translocation of gut organisms in neutropenic patients is around 27.4% (Liss et al. 2012). Overall, 50% of patients with neutropenia develop sepsis, whereas 20–30% and 5–10% develop severe sepsis (acute onset organ dysfunction or signs of hypoperfusion caused by sepsis) and septic shock (severe sepsis or hypotension without adequate fluid resuscitation and exclusion of other causes for hypotension), respectively (Penack et al. 2014).

14.3 Etiology and Pathophysiology

There are a myriad of causes of neutropenia which may range from congenital neutropenia which is rare compared to acquired causes that commonly includes drugs, nutritional, sepsis, malignancy and its treatment, bone marrow failure, autoimmunity induced neutropenia; Table 14.1 illustrates the common causes predisposing to neutropenia (Gibson and Berliner 2014). Noteworthy is the fact that some of these conditions may cause mild neutropenia and may not predispose the patient to life threatening infections. Other conditions like neutropenia secondary to hematological

Table 14.1 Causes of neutropenia

Congenital Neutropenia	Acquired Neutropenia				
	Infections associated	Drug induced	Malignancy	Autoimmune	Nutritional
Constitutional	Viral	Chemotherapy	Acute Leukemia	Primary autoimmune	Vitamin B12 deficiency
Ethnic	Varicella	Monoclonal antibodies	Myelodysplastic syndrome	Secondary autoimmune	Copper deficiency
Benign familial neutropenia	Measles				
	Rubella		Chronic lymphocytic leukemia	Felty syndrome	Global malnutrition
	Hepatitis	Antibiotics		Aplastic anemia	Folate deficiency
Cyclic neutropenia	EBV	Antifungals			
	HIV	Anti-psychotics	LGL leukemia		
	Bacterial	Anti-epileptics	NK/T cell leukemia		
	Brucella	Diuretics			
	Rickettsia	Cardiovascular drugs	Solid cancers		
	Mycobacteria				
	Others	Others			

Table 14.2 Drugs known to cause neutropenia

Antibiotics	Semisynthetic penicillins
	Cephalosporins
	β-lactams
	Vancomycin, Linezolid
	Dapsone
	Macrolides
	TMP-SMX
	Chlormaphenicol
Antifungal	Amphotericin B
Antiviral	Valganciclovir
Antimalarial	Chloroquine
	Quinine
Anti-psychotics	Clozapine
	Olanzapine
	Phenothiazines
Anti-thyroid	Propyl thiouracil
	Methimazole
Anti-epileptics	Carbamazapine
	Valproate
	Phenytoin
Anti-inflammatory	Ibuprofen
	Diclofenac
	Indomethacin
	Sulfasalazine
Diuretics	Thiazides
	Furosemide
	Spironolactone
	Acetazolamide
Antiarrythmics	Procainamide
	Flecainide
Othet cardiovascular drugs	Digoxin
	ACE inhibitors
	Propranolol
H2 blockers	Ranitidine
	Cimetidine
Anti-helminthics	Levamisole
Chelators	Deferiprone

malignancy, chemotherapy and radiotherapy used to combat the malignancy, bone marrow failure may predispose to life threatening infections with a high risk of mortality. Sepsis itself and the management of sepsis may further aggravate marrow suppression leading to profound and prolonged neutropenia. The degree and duration of neutropenia are the main denominator in determining the probability and severity of infection, a host may encounter. Patient in an ICU is at the mercy of a wide range of drugs, and a fair idea of the drugs known to cause neutropenia is essential. Table 14.2 illustrates a few common drugs used in ICU but are known to further complicate

neutropenia and requires review during management of a patient (Ibáñez et al. 2005). Apart from the prescribed drugs, there may be use of over-the-counter drugs, herbal and Ayurvedic medications, the risk of neutropenia associated with which is not well documented and should be kept in mind when a patient is being worked up. Another aspect to be kept in mind is a condition in which there is normal ANC but functional defect in neutrophil leading to primary immune deficiency. A few common conditions which needs consideration are hyper IgE syndrome, Chédiak–Higashi syndrome, neutrophil specific granule deficiency, chronic granulomatous disease, leucocyte adhesion defects, and myeloperoxidase deficiency (Dinauer 2007).

Not all the conditions mentioned above predispose the host to severe infections. Apart from the few conditions predisposing to severe infection as mentioned above, most other causes of neutropenia are usually mild and recover once the offending agent or cause is identified and treated. Fortunately, most of the cases are due to these relatively non-severe causes. These conditions need to be identified so as to avoid inadvertent investigations and overzealous treatment which may escalate the cost of treatment and predispose to further drug toxicity.

Neutropenia predisposes the individual to a wide range of infections, particularly bacterial and fungal. There has been a global shift in the pattern of organisms responsible for severe infections. Gram negative organisms were the major pathogens causing fever in neutropenic patients in the 7th–8th decade of the previous century. Thereafter, there was emergence of gram positive organisms probably due to use of more intense chemotherapy in cancer patients causing mucositis and gram positive colonization, use of indwelling central venous catheter during the course of chemotherapy and use of fluoroquinolone prophylaxis responsible for control of gram negative organisms (Viscoli et al. 2005). However, since the early part of this century, there is a resurgence of gram negative organisms. Gram negative organisms have been isolated in 50–60% patients with febrile neutropenia from different parts of the Indian subcontinent in recent times (Babu et al. 2016; Mandal et al. 2015). Similar trend is seen in neutropenia following bone marrow transplant where gram negative organisms outnumber gram positive organisms (72.7% vs 27.3%) (George et al. 2006). The reason for this resurgence could be explained by development of resistance to fluoroquinolones, which was extensively used for prophylaxis during chemotherapy induced neutropenia, and emergence of multidrug resistance (MDR) organisms and β-lactamase producing organisms (Lee et al. 2016). The primary concern at present is the emergence of MDR gram negative organisms. Defining MDR is also challenging. The European Centre for Disease Prevention and Control has defined the term MDR as "resistant to three or more antibiotic classes" (Magiorakos et al. 2012). However, due to the lack of uniform testing policy by a laboratory, this approach is impractical at times. The British Society for Antimicrobial Chemotherapy/Healthcare Infection Society/British Infection Association Joint Working Party defined MRD organism as a bacterium susceptible to only one or with no readily available oral agent active against the infections. Susceptibility to oral agents that have no parenteral form was not taken into account. Considering the paucity of newer antibiotics against gram negative organisms, MDR was proposed for isolates where only two, or fewer, unrelated antibiotics were active. Following

this definition, as a rule of thumb *Acinetobacter baumannii, Klebsiella* spp., *Enterobacter* spp., *Serratia* spp., and *Citrobacter* spp. that are susceptible to two or fewer of carbapenems, third-generation cephalosporins, including in combination with β-lactamase inhibitors, piperacillin/tazobactam, tigecycline, aminoglycosides, quinolones, or colistin are regarded as MDR and *E. coli* that is susceptible to two or more of carbapenems, ceftolozane/tazobactam, ceftazidime/avibactam, colistin, and fosfomycin but resistant to unprotected third-generation cephalosporins, co-amoxyclav, piperacillin/tazobactam, quinolones, and trimethoprim would not be an MDR (Hawkey et al. 2018).

Risk of invasive fungal infection (IFI) increases with the depth and duration of neutropenia. Fungal infections are *possible* when there is persistence of fever for more than 96 h in a neutropenic patient, *probable* when apart from clinical suspicion, there is radiological evidence or presence of serum biomarkers suggestive of an IFI and *proven* when there is a tissue diagnosis suggesting IFI. Hammond et al. in a retrospective study showed that 13.4% of patients with acute leukemia on prophylaxis developed IFI, 10.4% within the first 100 days after diagnosis of the leukemia. The cumulative probability of developing IFI was 5.9% by 30 days and 11.1% at 100 days after diagnosis of acute leukemia (Hammond et al. 2010)**.** Another analysis from the Mayo Clinic on the incidence of IFI in patients with acute leukemia and myelodysplastic syndrome on primary prophylaxis with voriconazole showed an overall incidence of 14.5%. The incidence of IFI was 2.4, 4.2, and 7.8 per cent for proven, probable, and possible infection, respectively (Barreto et al. 2013). Auberger et al. reported that incidence of IFI in hematological malignancy was 15%, where 90% of the cases were due to moulds and 10% due to yeasts. IFI was the principal cause of death in 35% patients and the risk was significantly higher in probable or possible IFI than proven IFI (37% and 38% vs 28%, $p = 0.019$) (Auberger et al. 2008)**.**

14.4 Clinical Features

A neutropenic patient, in sepsis may be febrile (core temperature >38.3 °C) or hypothermic (core temperature <36 °C). Breach in the mucosal barrier may cause oral ulcer and severe mucositis resulting in pain abdomen, predominating in the right iliac fossa. Diarrhea and ileus due to typhlitis may be present. Pain in the throat, cough, pleuritic chest pain, perianal pain due to ulcers, soft tissue infections, pain and tenderness along the central venous catheter tract may be present. There may be presence of pallor and bleed secondary to myelosuppression. Icterus secondary to liver dysfunction may be present. The patient may develop altered mentation, tachycardia, and tachypnea. In severe infections, patient may develop hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <65 mmHg), hypoxemia, acute oliguria (urine output <0.5 mL/kg/h for ≥2 h) leading to increased creatinine level (Penack et al. 2014)**.** The clinical symptoms depend on the foci of infections and the associated co-morbidities. A thorough clinical evaluation, preferably with a checklist, is imperative for rationalization of investigations.

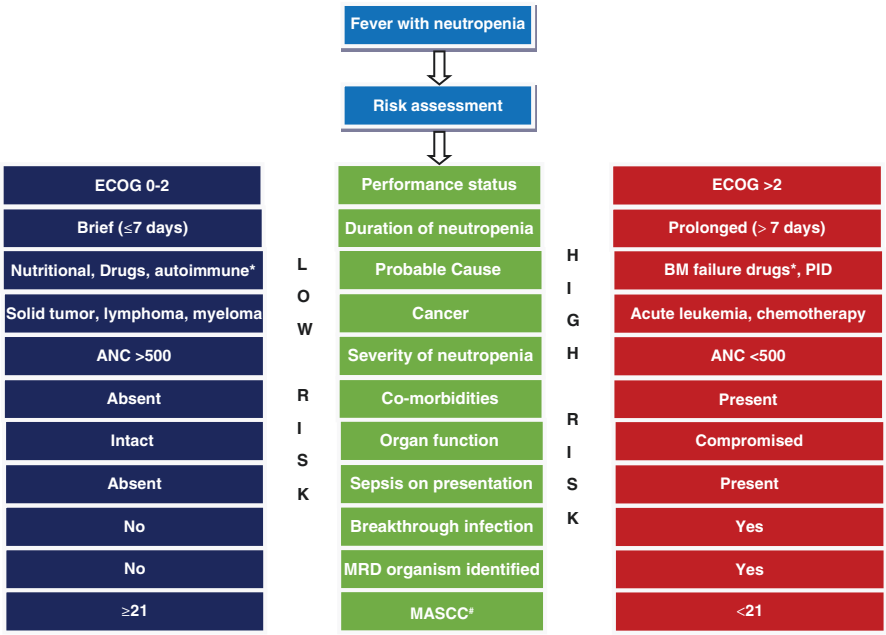
14.5 Approach to a Patient with Possible Differential Diagnosis

Evaluation of a patient with neutropenia should begin with a detailed history. Congenital causes of neutropenia and primary immunodeficiency may be ruled out by browsing the previous reports and assessment of history of recurrent infections requiring treatment with antibiotics. A careful assessment of fever, rash, pain abdomen, loss of appetite, nausea, vomiting, jaundice, exposure to blood products or high risk behavior preceding the neutropenia establish a viral infection related etiology. Viral infections may render the patient immunocompromised and may predispose to severe secondary infections. Nutritional deficiency may be associated with neutropenia but seldom leads to severe infection and should not be considered a sole cause of infection in a neutropenic patient. Association of neutropenia with an autoimmune etiology, especially rheumatoid arthritis and systemic lupus erythematosus should be considered. These conditions themselves or the drugs used for their treatment may cause significant neutropenia predisposing to life threatening infections. Anecdotal association of neutropenia with institution of a drug is of utmost importance in the ICU and careful review of all the medications to which the patient was exposed may help trace the cause. The importance of idiosyncrasies as a cause of neutropenia should be considered and any clinical suspicion should warrant temporary suspension of the clinically suspected offending agent. The incidence of non-chemotherapeutic drug induced neutropenia is 2.4–15.4 cases per million population. Affected patients may experience severe neutropenia within weeks to several months after first exposure to a drug, with a mortality rate as high as 5% (Curtis 2017)**.**

A detailed history and examination to elicit site specific symptoms to locate the foci of infection should be undertaken. Careful examination of skin (site of catheter entry, bone marrow aspiration site, any previous procedure site), alimentary tract, oral cavity or oropharynx, perineum and perianal region, thorax should be undertaken as these are the most common sites of colonization. History of previosuly documented colonization (surveillance), prior prophylaxis, associated comorbidities, and coexistent non-infectious causes of fever should be elicited. Another important aspect is drug or intravenous fluid infusion or blood product transfusion related fever which should be kept in mind before initiating search for a pathogen as a cause of fever.

14.6 Diagnostic Evaluation and Work-Up

It is imperative to stratify the patient into risk groups prior to planning work-up. An approach to stratify the patient is proposed in Fig. 14.1. A new prognostic model was proposed for chemotherapy induced febrile neutropenia based on age (≥60 years), procalcitonin level (≥0.5 ng/mL), ECOG performance status (≥2), oral mucositis (≥grade 3), systolic blood pressure (<90 mmHg), and respiratory rate (≥24/min). This model divided the patients in 3 class with significant difference



*Drugs and immune causes may cause variable degree of neutropenia and the stratification should be based on clinical judgment
#Multinational Association for Supportive Care in Cancer Risk-Index Score

Fig. 14.1 Risk assessment model for planning work-up and treatment

between the incidence of bacteremia and adverse event rate, and this model appears to be an interesting way of triage (Ahn et al. 2016).

There are two components in the work-up of a patient presenting with neutropenic fever in ICU. First is the identification of cause and foci of infection leading to the fever and second is the assessment of the cause of neutropenia. There can be a significant overlap between the two objectives and at times, the etiology of fever may be the primary cause of neutropenia and not infection. Rationalization of investigations based on the history and clinical finding is imperative (Figs. 14.2 and 14.3).

Blood cultures should be obtained with adequate sampling to identify the pathogen. Documentation of infection helps in specifically targeting the pathogen. Infections where pathogen is identified has a higher risk of mortality (mostly due to gram negative MDR sepsis) and requires prompt and effective therapy based on sensitivity report to improve outcome (Lyman and Rolston 2010). Most of the patients in ICU have a central venous access device and two sets of cultures, one from the central venous catheter and other from the peripheral vein should be obtained prior to the initiation of empirical antibiotics, as no growth may be found in the culture within minutes of antibiotic administration (Levy et al. 2018). For pediatric patients, the total volume of blood sampling should be limited to 7 mL per 10 kg body weight. A set of two blood cultures detect 80–90% and three or more cultures detect more than 96% of the blood stream pathogens (Cockerill et al. 2004;

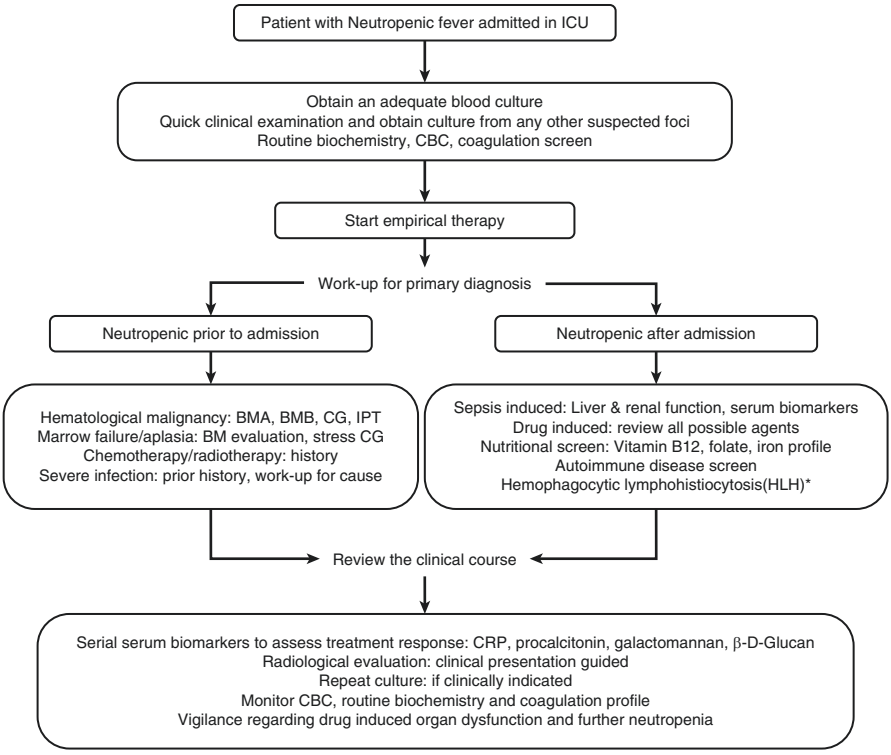
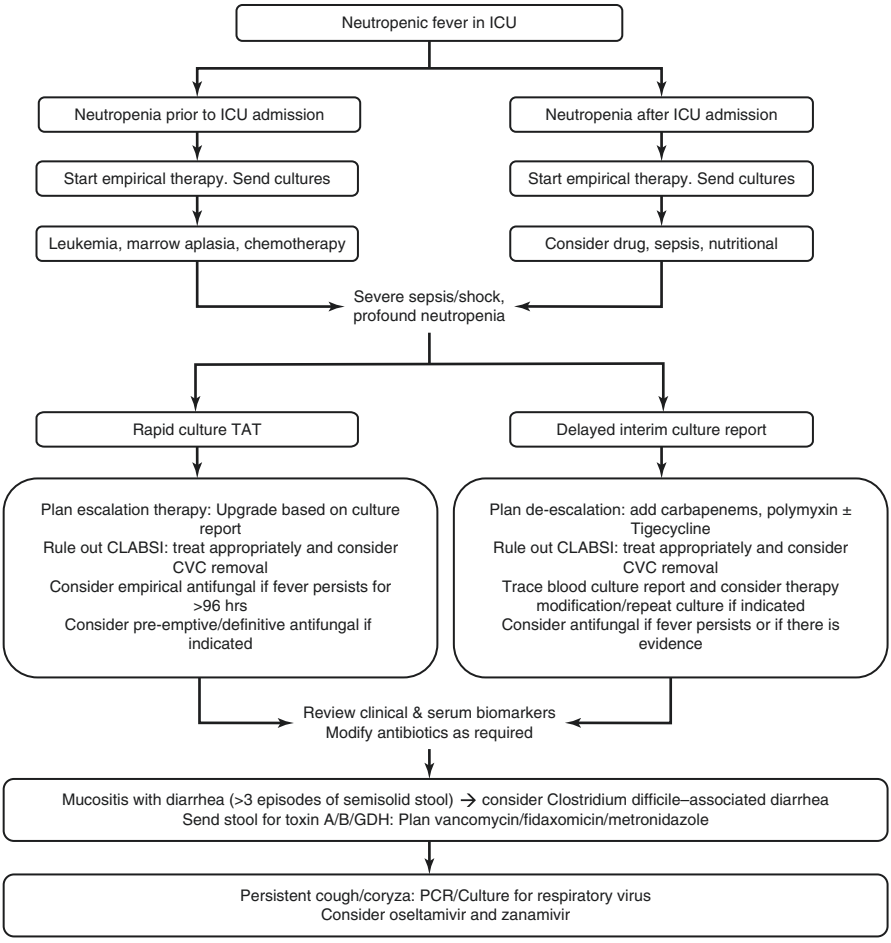


Fig. 14.2 Approach to diagnosis and monitoring

Lee et al. 2007). However, the timing of collection also matters, and in an interesting observation, it was seen that positive yield was 26.7% less when the culture sample was collected on a weekend or holidays and the number of positive cultures declined with repeated sampling and these may be non-modifiable confounders to a positive yield (Morton et al. 2015). Central line associated blood stream infections (CLABSI) is a very common source of infection in neutropenic patients. CLABSI is defined as a quantitative blood culture colony count ratio of 5:1 between central venous catheter and peripheral blood, but this ratio varies from 3:1 to 10:1 according to various reports in literature. Another concept to define CLABSI is differential time to positivity with blood culture sample from central venous catheter showing growth 2 h prior to the culture obtained from peripheral blood (Seifert et al. 2003). Positive culture from the catheter tip also qualifies as CLABSI. Incidence of CLABSI is reported as 2.1 per 1000 catheter days for respiratory ICUs and 5.1 for medical-surgical ICUs (National Nosocomial Infections Surveillance System 2004). Attempt to obtain procalcitonin guided blood culture in ICU was shown to be non-inferior to unguided culture in terms of infection related mortality at day 20 and 90,



TAT: Turn-around time; PCR: polymerase chain reaction

Fig. 14.3 Approach to management

limiting the benefit of procalcitonin as a guide to obtaining culture (van der Geest et al. 2017). Bacteremia associated with catheter related infections has shown variable results in terms of the organism responsible (Parameswaran et al. 2011; Gopalakrishnan and Sureshkumar 2010; Patil et al. 2011). Both gram positive and gram negative organism may colonize. *Klebsiella pneumonia*, *coagulase-negative staphylococci, Pseudomonas aeruginosa*, *Acinetobacter baumanii, and E. coli* are commonly reported pathogens. Fungal infection related CLABSI occurs commonly with yeasts and infection with candida spp. is reported with variable incidence ranging from 11.7% to 16% *(*Parameswaran et al. 2011*;* Pawar et al. 2004*)*. Apart from blood, culture should be obtained from all suspected foci of infection with an attempt to isolate an organism and target it appropriately. All catheters placed at any site of the body should be subjected to culture and sensitivity on removal. This may

serve as a guide to therapy during the present or future episodes of neutropenic sepsis. For intubated patients, culture should be obtained from the endotracheal tube. Another challenge in ICU is to differentiate infectious from non-infectious cause of fever. Biomarkers come to our rescue many a times and a meta-analysis has shown procalcitonin to be more sensitive (88% vs 75%) and specific (81% vs 67%) than c-reactive protein in differentiating infectious from non-infectious fever (Simon et al. 2004). Procalcitonin guided antibiotic policy has shown to reduce the duration of antibiotic exposure and subsequently antibiotic associated toxicities (Schuetz et al. 2018), but do not have a significant impact on mortality (Schuetz et al. 2017). These biomarkers can thus be used as a clinical decision aid and should never override clinical judgment.

A neutropenic patient is at high risk of developing invasive fungal infections (IFI) and vigilance with high index of suspicion is required to plan a workup to document the same. A proven fungal infection requires histological, cytological, direct microscopy or culture based recovery of the yeast or mould. In a neutropenic patient, obtaining sample by invasive intervention may be difficult. In a susceptible host, clinically documented lower respiratory tract infection not responding to antibiotics, tracheobronchitis, sinonasal or CNS infection with radiological evidence in the form of cavity or air-crescent or halo sign on CT thorax, evidence of sinusitis, meningeal enhancement of MRI or CT, target like bull's eye lesion in liver or spleen or progressive retinal exudates on ophthalmologic examination, may be suggestive of fungal infection. Demonstration of galactomannan in plasma, serum, bronchoalveolar lavage fluid, or CSF or β-D-glucan in serum are useful biomarkers for probable detection of aspergillosis or candidiasis. The interpretation index for galactomannan was set at 1.5 in Europe which was lowered to 0.5 by the FDA, while for β-D-glucan, a cutoff of ≥80 pg/mL gives a specificity of 89–93% (De Pauw et al. 2008; Talento et al. 2017; Huppler et al. 2017). Detection of nucleic acid antigen of fungal cell wall is a promising option for diagnosis of IFI. Although not included in the 2008 EORTC/MSG consensus recommendations due to lack of validation studies, there are recent systematic reviews showing that the data is mature enough to warrant inclusion of PCR based tests in EORTC/MSG guidelines (White et al. 2015).

Along with the diagnosis and documentation of infection, diagnosis of the primary etiology for neutropenia is essential. Careful examination of the complete blood count with peripheral smear may give a clue to the cause of neutropenia and may guide further diagnostic plan. For congenital causes of neutropenia, documenting the absolute neutrophil count at different timepoints may give a clue to the etiology which can be confirmed by specific molecular studies. Bone marrow examination with immunophenotyping and karyotyping are required in suspected cases of hematological malignancy. Infectious etiology requires specific serum bioassays or nucleic acid antigen detection. Nutritional status work-up in the form of vitamin B12 and folate are essential. These may not explain the cause of neutropenic fever but may be associated with response to therapy and their deficiency may lead to delayed neutrophil recovery. Autoimmune disease screen should be undertaken for documentation of secondary immune mediated neutropenia. For functional

neutropenia, B and T-lymphocyte subset analysis, serum immunoglobulin titre, and specific assays like nitroblue tetrazolium or dihydrorhodamine assay may be indicated on samples from the patient, sibling, and parents. Routine biochemical assay is essential, which may give a clue to diagnosis as well help in monitoring sepsis or treatment associated organ compromise if any.

14.7 Management

There are two components in the management of neutropenic sepsis. Aggressive management of sepsis and management of the cause of neutropenia. It is important to ascertain if the patient was neutropenic prior to admission in the hospital or (s)he became neutropenic during the course of treatment. Charting of the neutrophil count during the entire course of stay in the hospital gives a fair clue regarding the same. Before discussing the management with regard to antibiotics and antifungals, let us define the types of treatment options. *Prophylaxis* is the form of therapy which is started prior to encountering infection and considered in patients with anticipated prolonged and profound neutropenia like those planned for intensive induction chemotherapy. *Empirical therapy* is started on the basis of clinical evidence of sepsis in a neutropenic patient and is usually the initial form of treatment until investigation reports are available; *Pre-emptive therapy* is based on some form of evidence of the infection like a serum biomarker or radiological evidence apart from the clinical findings; while *definitive treatment* is based on establishment of tissue diagnosis and demonstration of the organism in culture and includes sensitive agents targeting the organism (Leekha et al. 2011).

A patient entering the ICU may be either febrile from before and already on empirical therapy, or may develop fever after admission and may or may not be on prophylactic therapy. The latter is usually true in patients who develop neutropenia during the course of stay in the hospital secondary to drugs, sepsis, and nutritional deficiency. This should be considered prior to planning a change in therapy to avoid over treatment.

The greatest risks of severe sepsis are in patients who are neutropenic secondary to marrow failure, hematological malignancy, and cancer chemotherapy. These are the patients who are usually put on prophylaxis and started on empirical broad spectrum therapy on the first encounter with fever. In case a patient is not on empirical therapy, it is prudent to obtain surveillance cultures from stool, throat, and skin and this may be guide to therapy. However, it is important to remember that blood stream infections may grow organisms different from the organisms grown on surveillance culture (McGinigle et al. 2008). Another important aspect is the time lag between first encounter with fever and starting empirical therapy and studies have shown that 1-h delay in initiation of antibiotic may increase the risk of 28-day mortality by as much as 18% (Rosa and Goldani 2014). Reasonable first line treatment options includes a broad spectrum agent with anti-pseudomonal activity. Piperacillin-tazobactam, cephalosporines like cefoperazone–sulbactam, cefipime, ceftazidime with or without an aminoglycoside, and carbapenems like meropenem or

imipenem–cilastatin are reasonable options (Horita et al. 2017). However, it is to be remembered that the dosing schedule for neutropenic patients are either more frequent, or the concentration is higher, or the duration of infusion is prolonged. Optimization of the administration schedule is essential for effective results against the MDR organisms (MRDO). The main challenge facing an intensivist is to tackle the MDRO. With no new class of antibiotics in the pipeline, re-emergence of polymyxins has been a saving grace. Colistin is administered as an inactive pro-drug colistimethate sodium and demonstrates concentration-dependent bacterial killing, which has been utilized using colistin at a loading dose of 9 MIU and maintenance dose of 4.5 MIU twice daily with close monitoring of renal function (Kift et al. 2016). There is synergism between the activity of carbapenems and polymyxin (Zusman et al. 2013), and this have been used to treat patients in recent past, however, emergence of recent data from a randomized control trial (RCT) comparing combination of meropenem with colistin versus colistin monotherapy has shown that there is no difference in rate of clinical failure at day 14 (73% vs 79%) with higher incidence of toxicity in the combination arm (Paul et al. 2018). Another RCT comparing piperacillin–tazobactam with or without tigecycline in MRDO has shown that combination therapy has better chance of resolution of febrile episode (67.9% vs 44.3%) without significant difference in adverse effects and mortality (Bucaneve et al. 2014). Combination of carbapenems has been compared to monotherapy in MRDOs and combination of meropenem and ertapenem has shown lower 28-day mortality (29.2% vs. 47.9%, $p = 0.04$); higher rate of clinical cure (65% vs. 31.3%, $p = 0.03$) and microbiological eradication (57.9% vs. 25.9%, $p = 0.04$) (De Pascale et al. 2017). Combination therapy has shown significantly lower rate of 30-day mortality compared to monotherapy (54.3% vs. 34.1; $p = 0.02$) and triple combination with meropenem, colistin, and tigecycline was associated with lower mortality (OR: 0.11; 95% CI: 0.02–0.69; $P = 0.01$) in bacteremia due to carbapenemase producing Klebsiella pneumonia (Tumbarello et al. 2012). The expert Group of the fourth European Conference on Infections in Leukemia had developed guidelines on empirical antibiotic therapy in 2011, based on the local resistance pattern and the patient's risk factors. A *de-escalation approach* is advocated based on prior colonization or infection with resistant pathogens, complicated presentation, and in centers where resistant pathogens are prevalent and initial empirical combination antibiotic therapy to cover MDR strains is used. The antibiotics are de-escalated based on the culture report when available. *Escalation approach* is used in patients without significant risk factors in whom initial carbapenems and combination therapy are avoided. The initial antibiotic regimen is modified after 72–96 h and discontinuation of the antibiotic is considered after 72 h or later in patients who remain hemodynamically stable and afebrile for 48 h with no proven culture documented infection, irrespective of neutrophil count and expected duration of neutropenia (Averbuch et al. 2013). A recent RCT has re-emphasized that empirical antibiotic therapy can be discontinued after 72 h of apyrexia and clinical recovery irrespective of the neutrophil count (Aguilar-Guisado et al. 2017). Another study had shown that in carbapenem resistant organisms, initiation of *appropriate therapy* was associated with significant reduction in mortality (HR 0.45; 95% CI 0.33–0.62, $p < 0.0001$) than with early initiation of the therapy (HR 0.85; 95% CI: 0.59–1.21, $p = 0.35$) suggesting that the timing to target these organism should be guided by the clinical

Table 14.3 Indications of empirical gram positive antibiotic coverage in neutropenic sepsis

Hemodynamic instability or other evidence of severe sepsis
Radiologically documented pneumonia
Positive growth of gram positive organism before sensitivity report is available
Suspected CLABSI
Skin or soft tissue infection
Severe mucositis in patients with fluoroquinolone prophylaxis or empirical ceftazidime therapy

condition of the patient and by the local sensitivity pattern of the organism if the clinical condition of the patients allows the time required to do so (Gutiérrez-Gutiérrez et al. 2017). Unlike gram negative organisms, gram-positive organisms are usually not targeted empirically, with no significant difference in all-cause mortality (RR 0.90 (95% CI: 0.64–1.25) and equal overall failure at the end of therapy (RR 1.00; 95% CI: 0.79–1.27) in patients with or without empirical gram positive cover (Beyar-Katz et al. 2017). The few definitive indications to start empirical gram positive antibiotic coverage are summarized in Table 14.3. A bactericidal drug like vancomycin or teicoplanin is preferred over a bacteriostatic linezolid, except when evidence of colonization by vancomycin resistant organism is known, and the ultimate therapy should be based on the drug sensitivity report (Freifeld et al. 2011). Breakthrough infection such as Clostridium difficile-associated diarrhea is not uncommon in neutropenics and stool should be tested for toxin A, B and glutamate dehydrogenase or by nucleic acid amplification test in patients with ≥3 episodes of unformed stool in 24 h. Oral Vancomycin at a dose of 125 mg orally 4 times per day or Fidaxomicin 200 mg twice daily for 10 days is the recommended therapy and metronidazole can be used in non-severe cases only when there is no access to the former drugs. For fulminant infection, vancomycin dosage is 500 mg orally 4 times per day and 500 mg in approximately 100 mL normal saline per rectum every 6 h as a retention enema together with metronidazole (McDonald et al. 2018). Although there is no dearth of evidence available to guide antibiotic regimens, the antibiotic strategy should be decided based on the hospital infection pattern and antibiotic policy, so much so that a recent guideline proposes to use colistin with high dose tigecycline or aminoglycoside empirically if the local epidemiology and antibiotic policy suggests colonization by carbapenem resistant organisms (Hawkey et al. 2018).

Fungal infections are a major cause of sepsis in neutropenic patients who may be on prophylaxis with azoles targeting either candida spp. alone or with agents to cover mould as well. Fluconazole is used for the former and voriconazole or posaconazole for the latter. Breakthrough infections are common and should be promptly targeted to reduce mortality. If combination therapy is required, a reasonable combination based on the mechanism of drug action is an echinocandin with either a polyene or azole (Odds et al. 2003). With regard to the policy to initiate antifungals, debate on pre-emptive or empirical antifungal therapy is never ending with results backing both forms of treatment (Cordonnier et al. 2009; Fung et al. 2015; Hebart et al. 2009). The therapy should be based on the availability of resource and the turn-around time for reports, as well as the clinical condition of the patient. The European Conference on Infections in Leukemia (ECIL-6) guideline recommends Echinocandins or Liposomal Amphotericin B for candida spp. except candida parapsilosis where Fluconazole still remains a reasonable option. When

catheter colonization is suspected, it is recommended to remove the catheter. In situations where catheter removal is not possible, either an Echinocandin or Liposomal Amphotericin B should be used considering their better action on biofilms. For suspected aspergillosis, either Voriconazole or Isuvaconazole is preferred over Liposomal Amphotericin B whereas there is recommendation against the use of Amphotericin B deoxycholate (Tissot et al. 2017). Evidence supporting combination antifungal therapy is lacking at present. A RCT comparing Voriconazole with or without Anidulafungin failed to reach the primary endpoint of decreased all-cause mortality at week 6, but in a subgroup of patients with an invasive aspergillosis documented by positive galactomannan, 6-week all-cause mortality was lower in patients receiving combination therapy. Further studies are needed until combination therapy finds recommendation in the guidelines (Marr et al. 2015). For suspected mucorales, surgical debridement along with Liposomal Amphotericin B is recommended and Posaconazole due to its sensitivity and the ease of administration may be used as a maintenance therapy (Tissot et al. 2017).

G-CSF prophylaxis is recommended post chemotherapy neutropenia in regimens which have ≥20% risk of febrile neutropenia and usually not necessary for regimens with <10% risk. For regimens with 10–20% risk, the decision to use G-CSF is based on age of the patients and presence of co-morbidities (Freifeld et al. 2011). With regard to the type of G-CSF, there was no difference between long and short acting G-CSF in RCTs, while in non-RCT studies, long acting G-CSF showed lower risk of chemotherapy induced febrile neutropenia (Cornes et al. 2018). Granulocyte infusion has been used to treat neutropenic patients, and studies prior to 2000 has shown reduction in all-cause mortality (RR 0.53, 95% CI 0.33–0.85; *low-quality evidence*) for those receiving granulocyte infusion; but studies post 2000 have shown no difference in all-cause mortality (RR 1.10, 95% CI 0.70–1.73, *low-quality evidence*), and overall there was no difference in all-cause mortality over 30 days between participants receiving therapeutic granulocyte infusion and those who did not (RR 0.75, 95% CI 0.54–1.04). There was no difference in clinical reversal of concurrent infection in those receiving granulocyte and those who did not (RR 0.98, 95% CI 0.81–1.19) (Estcourt et al. 2016). However, there was difference in the protocol of granulocyte collection and infucion given to the patients in these trials. We feel that in the era of gram negative MDR sepsis with limited sensitive antibiotic options available, granulocyte infusion may emerge as a useful tool, provided well designed clinical trial with a standardized protocol of product collection and infusion, is conducted.

14.8 Future Directions

Emergence of MDRO is the challenge facing intensivists, oncologists, and hemato-oncologists dealing with neutropenic sepsis. Recent review questions the utility of prophylaxis in patients with anticipated neutropenia in the absence of strong evidence to support the same, fearing selection of resistant strains (Calitri et al. 2018). Recent study favors a review in antibiotic within 24 h, considering the fact that

92.1% of the positive blood culture are seen within this period and none of the MDRs grow after this 24 h bracket (Puerta-Alcalde et al. 2019). In the quest to tackle the MDROs, newer formulations of cephalosporine like the siderophore cefiderocol (Dobias et al. 2017), and combinations of new β-lactamase inhibitors with carbapenems and cephalosporins has shown promising results (Castanheira et al. 2017; Marshall et al. 2017; Gonzalez et al. 2017; Karlowsky et al. 2018). Development of newer class of antibacterials is an imminent need to strengthen the armamentarium against these resistant organisms.

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Management of Viral Infections in ICU

15

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Key Points
Viral infections, ICU.

15.1 Introduction

The modern day diagnostics have enabled the physicians to recognize viral infections in intensive care units more often. Many critical illnesses are being increasingly attributed to viral etiologies, in both community and hospital settings. Hitherto, it was believed that only immunosuppressed patients are afflicted with viral infections with severe outcomes. However, it has been progressively recognized that immunocompetent patients, especially with certain risk factors, may also get admitted to intensive care units with critical illnesses attributable to viral infections. Even though respiratory system involvement is most common, a neurological, cardiovascular or a multisystemic presentation may also be seen. An astute intensivist may recognize that a worsening in clinical status of patients admitted in intensive care units may be due to reactivation of certain viruses. It is imperative to think about viral infections, as a possible etiology and a differential diagnosis, in critically ill patients with new onset fever, failure to wean or multiorgan dysfunction. An inadvertent misdiagnosis of the etiological agent will translate into poor

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outcomes. Hence, it is indispensable to train the intensivist for early suspicion, diagnosis and management of viral illnesses in intensive care units. The aim of the present chapter is to sensitize the intensivist about viral infections which have the potential to cause life threatening illnesses requiring management in critical care units.

15.2 Epidemiology/Problem Statement

Viral infections are common self-limiting illnesses, which may quite often go unnoticed in a community. On the contrary community acquired viral infections may also lead to life threatening manifestations in patients with certain risk factors, which may require intensive care management.

Respiratory viruses may be held accountable for 5–10% of patients with community acquired pneumonia (CAP) and one third of patients with severe pneumonia. Even though influenza virus (type A and B) and rhinovirus are the most common virus isolated, these are still underdiagnosed in critically ill patients. The other respiratory viruses which may cause CAP are parainfluenza, rhinovirus, adenovirus, respiratory syncytial virus (RSV), coronavirus, and human metapneumovirus. Community acquired pneumonia (CAP) due to these viruses may progress on to develop acute respiratory distress syndrome (ARDS), the exact incidence of which is not yet known. Cytomegalovirus (CMV), influenza (human, avian, swine), and adenovirus are the 3 most common causes of severe viral CAP in immunocompetent adults. A new addition to the list of viruses is the SARS-CoV-2, the etiological agent for COVID-19 described recently. Around 40% of acute exacerbations of chronic obstructive airway disease (COPD) leading to cardiorespiratory failure and ICU admissions have been documented to be caused by respiratory viruses. Significantly, 16–49% of patients with acute respiratory failure or unspecified lower respiratory tract infections needing critical care management have viral etiologies. Respiratory viruses may even be isolated in 39% of critically ill patients with polymicrobial infections.

Similarly nosocomial reactivation of latent viruses, like Herpes virus (HSV) and CMV, may progress on to develop a severe illness in already critically ill patients, ranging from unexplained fever to weaning failure. Other than herpesviridae group of viruses influenza, parainfluenza, rhinovirus, metapneumovirus, RSV, and adenovirus may also be accountable for nosocomial infections in critically ill patients. Acanthamoeba polyphaga mimivirus (mimivirus) has been hypothesized as a possible etiological agent for nosocomial ventilator associated pneumonia (VAP). However, there is not enough evidence so far to support this hypothesis. Fortunately observational studies have shown that the respiratory viruses have a very limited role to play as a causative agent for nosocomial pneumonia. It has been reported that only <5.5% of critically ill patients on mechanical ventilator develop VAP, due to one of the respiratory viruses.

Table 15.1 Viruses causing AES

DNA viruses	HSV, VZV, HHV 6, EBV, adenovirus, parvovirus, CMV
RNA viruses	JE, WNV, dengue, CHIKV, enterovirus, MMR, chandipura, Nipah, KFD, rabies, HIV, LCMV

HSV herpesvirus, *VZV* varicella zoster virus, *HHV 6* human herpesvirus 6, *EBV* Epstein Barr virus, *CMV* cytomegalovirus, *JE* Japanese encephalitis, *WNV* west Nile virus, *CHIKV* chikungunya virus, *MMR* measles-mumps-rubella, *KFD* Kyasanur forest disease, *HIV* human immunodeficiency virus, *LCMV* lymphocytic choriomeningitis virus

Cytomegalovirus infection is common in community with increasing seroprevalence with age of infected individuals. The seroprevalence of CMV infections increases from 65% in the fourth decade of life to 91% in ages more than 80 years. Among critically ill patients, 0–36% may develop CMV infection, which may be primary or reactivation. Higher incidence of reactivation is seen in septic patients with high disease severity and ICU stay more than 5 days. Similarly, 45–56% of burn patients may demonstrate fourfold rise in serological titers of CMV or CMV viremia suggesting reactivation. Cytomegalovirus infection develops mostly between 4 and 12 days after ICU admission. The highest viremia in patients requiring intensive care is seen after a median stay of 26 days in ICU. Even though CMV infection may be asymptomatic in immunocompetent, it leads to unexplained fever, infectious mononucleosis like presentation, severe CAP, and postperfusion syndrome in critically ill patients.

It has been observed that HSV bronchopneumonitis, just as CMV, involves critically ill patients who are being mechanically ventilated, with ARDS, with burns or after surgery. Herpesvirus may get reactivated in about 54% of patients who are being mechanically ventilated. This reactivation usually takes early during the stay in ICU. Interestingly, 56% of these patients with HSV reactivation are asymptomatic and the remaining may be associated with gingivostomatitis or herpetic ulceration of the lip. Herpesvirus bronchopneumonitis usually occurs in patients on mechanical ventilation after a mean of 14 days. Even 21% of patients with VAP and 30% of patients with ARDS may be attributed to herpesvirus.

Many a time, isolation of viruses does not mean causal association. Isolation of these viruses in critically ill patients is usually associated with higher mortality rate which is similar to that of bacterial infections. It is still not clear whether these outcomes are directly related to viral etiology or they are just a marker of disease severity.

The etiologies of acute encephalitis syndrome include infectious and noninfectious etiologies. The infectious etiologies include viruses, bacteria, fungi, and parasites. The viruses responsible for acute encephalitis syndrome (AES) in India have been tabulated as follows (Table 15.1).

Herpesvirus is one of the most common viruses causing sporadic encephalitis. In India, Japanese encephalitis (JE) virus is the most common virus causing acute encephalitis in northern, northeastern, and southern India. It has been estimated that approximately 7500 annual JE cases may be seen in India in the event of an epidemic, with a morbidity rate of 0.3–1.5 in a population of 1,00,000.

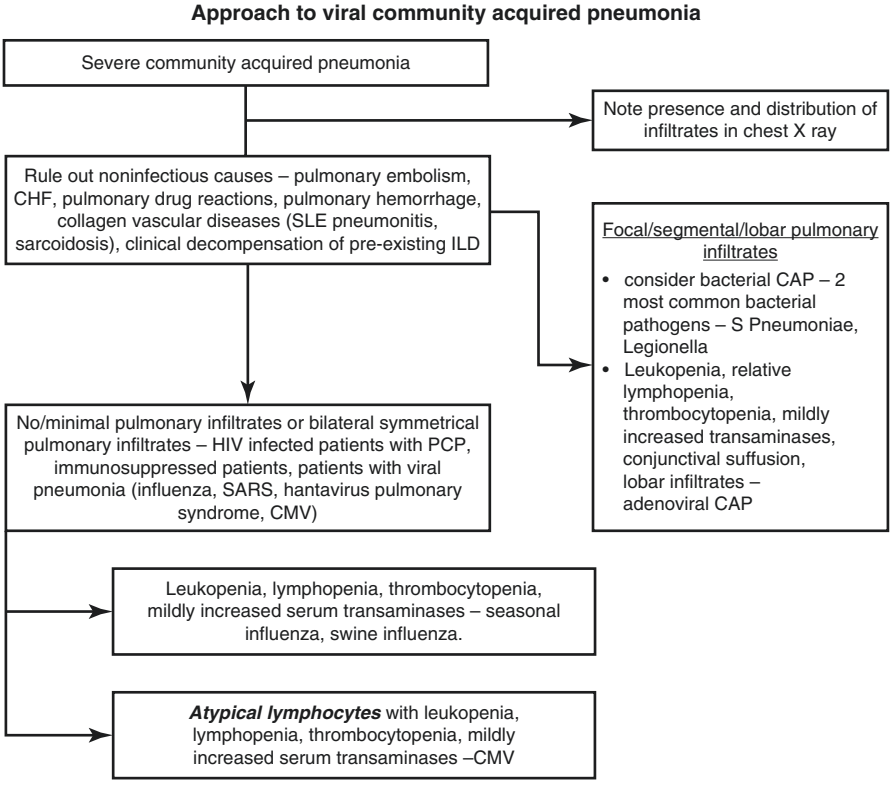
As far as viral hemorrhagic fevers are concerned, India is endemic to dengue and Kyasanur forest disease. Dengue fever is found to occur throughout the country except some higher mountainous reaches. Kyasanur forest disease (KFD) is found to occur predominantly in the 5 districts of Karnataka state, namely Shimoga, Chikkamagalore, Uttar Kannada, Dakshina Kannada, and Udupi. Seasonal outbreaks of KFD are known to occur from January to June. Epidemiological investigations have found seropositivity for KFD from neighboring states of Tamil Nadu and Kerala as well. Recently, an outbreak of Crimean–Congo hemorrhagic fever (CCHF) was noted to occur in Ahmedabad where four deaths were reported due to this hemorrhagic fever. Hantavirus has also been occasionally reported from few parts of the country. Thottapalayam virus, the first hantavirus, was reported from Vellore in the year 1964. Seroepidemiological studies from Southern India have found out that 14.7% of fever cases may be positive for hantavirus serology. Among the healthy blood donors, 5.7% were positive for hantavirus in the same study.

15.3 Approach to the Patient

The clinical features of viral infections in the ICU are nonspecific and very similar to those of bacterial or fungal infections. Thus, a very high index of suspicion may be required to consider viral infection as a differential diagnosis. It is imperative to make an etiological diagnosis so as to provide targeted therapy to the critically ill. Lately, the targeted microbiological investigations have reduced the uncertainties in making a diagnosis.

Certain clinical variables may predict the possibility of viral etiologies, such as immunosuppressed status, use of corticosteroids >10 mg/day for 3 weeks, use of other immunosuppressives, ground glass attenuations on pulmonary CT scans, increased duration of hospital/ICU stay, mechanical ventilation, and late onset VAP. Out of these, immunosuppression and ground glass attenuation are most prominent on multivariable analysis.

The intensivist should consider screening for CMV in all critically ill patients with fever and involvement of one or more organs, with no other explanation for their clinical status. Patients with unexplained ARDS and pneumonia should be evaluated for HSV and CMV infections. Clinicians should remember the possibility of HSV pneumonia/HSV associated ARDS, in appropriate patients, if they have associated herpes labialis or gingivostomatitis. All acute respiratory infections should be evaluated for influenza virus during influenza season. HSV may get reactivated due to trauma of intubation or mechanical ventilation. This may later lead to late onset VAP, which may present as unexplainable weaning failure. Unlike HSV associated late onset VAP, late onset VAP attributable to CMV occurs very infrequently. Critically ill patients with ground glass opacification on pulmonary CT scans, in appropriate settings, should be assessed for respiratory viruses. Besides, the viral etiologies may be considered in clinical settings other than mentioned here, if deemed fit by the treating clinician. An algorithm regarding approach to viral CAP is suggested in this review (Algorithm 15.1).



Algorithm 15.1 Approach to viral community acquired pneumonia

The viral infections are usually self-limiting, however, they may have worse outcomes in critically ill patients with risk factors. Outcomes of viral infections in critically ill patients may be similar to those of bacterial infections. These two groups of patients may have similar 28 days mortality rates, severity of illness, duration of mechanical ventilation or duration of ICU stay. However, patients having both bacterial and viral respiratory infections may end up with worse disease severity than patients with only one of them. Hence, even after identification of a virus, concern about a bacterial coinfection still persists. This concern makes it difficult for the clinician to limit use of antimicrobials.

15.4 Clinical Features

As already mentioned, viral infections have nonspecific clinical presentations which may be difficult to differentiate from bacterial or fungal infections. Even the severity and clinical course of viral respiratory infections is comparable to that of

Table 15.2 Respiratory virus profile in community acquired and nosocomial settings

Community acquired	Endogenous	HSV, CMV
	Exogenous	Influenza, parainfluenza, adenovirus, rhinovirus, RSV, coronavirus, metapneumovirus
Nosocomial	Endogenous	HSV, CMV
	Endogenous	Mimivirus, CMV (transfusion), H1N1 pandemic influenza

bacterial and fungal infections. Immunocompromised patients have a more complicated course of illness as compared to immunocompetent. Whereas, an "atypical" pneumonia presentation may be seen in immunocompetent, severe lobar or bilateral pneumonia may be seen in immunocompromised hosts. These infections may be acquired either in community or nosocomial settings. The respiratory virus profile in these two settings is different as detailed in the following table (Table 15.2).

The respiratory viruses are responsible for many of the community acquired infections. Patients afflicted with respiratory viruses present with nonspecific complaints. The nonspecific symptoms may include fever, chills, arthralgia, myalgia, headache, vomiting, diarrhea, otitis, tonsillitis, keratitis, and conjunctivitis. The respiratory symptoms may comprise of cough, rhinorrhea, and shortness of breath. There may be extra pulmonary involvement as well, such as inappropriate secretion of antidiuretic hormone, neurological abnormalities, hepatitis, encephalitis, meningitis, transverse myelitis, Guillain–Barré syndrome, and myocarditis. In particular, hemorrhagic cystitis may be found with adenoviral affliction mostly in immunosuppressed. Herpes simplex virus may have associated gingivostomatitis, keratitis, conjunctivitis, herpetic lip ulcerations, and genital herpes. The respiratory viruses usually lead to a self-limited mild illness in immunocompetent patients, which may quite often go undetected. On the contrary, fulminant forms of viral pneumonia may be seen in certain category of immunosuppressed patients with risk factors, such as morbid obesity, diabetes, pregnancy, hemoglobinopathy, atherosclerotic disease, congestive heart failure, asthma, cystic fibrosis, COPD, cirrhosis, and chronic renal failure. Significantly, patients with CMV associated community acquired pneumonia (CMV-CAP) may present with long standing fever without any prominent respiratory symptoms. Thus, a high index of suspicion is required to diagnose CMV-CAP. Associated hypoxemia may be present in severe viral CAP. Many of these presentations will require organ support in ICU settings.

As against the community acquired infections, nosocomial viral infections in the intensive care unit are usually caused by reactivation of viruses like herpes virus (HSV), Epstein Barr virus (EBV), and CMV. These viruses can get reactivated in critically ill patients with one or more of the following risk factors—mechanical ventilation, bacterial pneumonia, corticosteroid use, sepsis, shock, burn, trauma, blood transfusion, postsurgery, chronic renal failure, and extremes of age. Reactivation may be followed by a disseminated or a localized disease. Even though HSV reactivation in throat happens in early ICU admission HSV induced bronchopneumonia happens later, after about a mean of 14 days of mechanical ventilation. These patients will have symptoms such as fever, hypoxemia, and purulent tracheal secretions. Reactivation of CMV in critically ill patients with any one of the

discussed risk factors may lead to severe manifestations or multivisceral involvement. The spectrum of systemic involvement due to CMV infection in critically ill patients includes interstitial pneumonitis, hematological disorders, hepatitis, gastroenteritis, colitis, myocarditis, meningoencephalitis, uveitis, and retinitis. The lung involvement is the most common. Transfusion associated CMV mononucleosis is one of the causes of new fever in critically ill adult patients. The median time to onset of CMV infection varies between 4 and 28 days. Epstein Barr Virus (EBV) may also show reactivation in critically ill patients after ≥5 days. In immunocompetent individuals EBV may present with fever, pharyngitis, headache, malaise, lethargy and may have associated lymphadenopathy and splenomegaly. Meningitis, encephalitis, hemolysis, splenic rupture may occur rarely. There are not many studies looking into the clinical presentation of EBV reactivation in critically ill patients. It has been suggested that EBV and CMV reactivation should be entertained as a cause of fever in critically ill patients without any specific fever related symptoms and with no response to conventional therapy. Similar to community acquired infections, nosocomial infections may also result in grave outcomes in immunosuppressed and critically ill immunocompetent patients. HSV and CMV may be isolated from mechanically ventilated patients and is associated with prolonged mechanical ventilation, ICU stay and increased mortality rate. Reactivation of EBV is associated with increased morbidity and mortality. Higher viral loads have higher incidences of these complications. However, a causal association between infection and poor outcomes has not been convincingly proven so far.

Complications may be seen more frequently in patients with risk factors. Besides, late consultation, lower respiratory tract lesions, and leukopenia are also associated with severity in H5N1 infections. Both community acquired and nosocomial viral infections may lead on to the development of ARDS. The “common” viruses which may cause ARDS include influenza viruses (H1N1, H5N1) and coronaviruses. Uncommonly, viruses causing nosocomial pneumonia such as HSV and CMV may also progress on to ARDS. Diffuse viral pneumonitis with severe hypoxemia/ARDS may be associated with shock, hepatic failure, and renal failure. Rapid worsening may be seen in influenza on day 4 or 5, with intubation often required within 24 h of admission. CMV infections in an immunocompetent patient may have complications such as thrombosis, disseminated intravascular coagulation (DIC) due to hemostatic abnormalities and portal venous thrombosis due to acute hepatitis. Immunomodulatory effects of CMV may lead to increased incidence of fungal and bacterial opportunistic infections (Tables 15.3 and 15.4).

15.4.1 Viral Infections of the Nervous System in the ICU

Viral infections of the central nervous system may cause any one of the following neurological syndromes—encephalitis, meningitis, meningoencephalitis, myelitis, polyradiculoneuropathy, Guillain–Barré syndrome, subacute sclerosing panencephalitis, and postinfectious acute disseminated encephalomyelitis. Patients with clinical features like seizures, altered sensorium, coma, and respiratory failure (due to

Table **15.3** ICU level requirements in various viral infections

Type of viral infection	Percentage of patients requiring ICU care (%)
Adenovirus	1
SARS-CoV-1/SARS-CoV-2	25/5
MERS-CoV	89
hMPV	6

Key: SARS-CoV, MERS-CoV, hMPV

Table 15.4 Case fatality rate for various viral infection

Type of viral infection	Case fatality rate (%)
SARS-CoV-1/SARS-CoV-2	9/5
Rhinovirus	30
Avian influenza (H5N1)	60
MERS-CoV	60
Viral meningoencephalitis (HSV encephalitis)	70 (<20% with treatment)
Viral hemorrhagic fever	Varies—1–90

Key: SARS-CoV, MERS-CoV

aspiration, neuromuscular weakness, and atelectasis) will require ICU support. Other clinical manifestations include fever, bizarre behavior, headache, disordered mentation, psychiatric symptoms, and localized neurological signs.

15.4.2 Viral Myocarditis in the ICU

Patients with viral myocarditis present with clinical signs and symptoms suggestive of congestive heart failure. Low perfusion state due to shock may lead to end organ damage, which in turn will need ICU management of patients.

15.4.3 Viral Hemorrhagic Fever in ICU

Clinical manifestations of viral hemorrhagic fever ranges from mild to life threatening illness. The symptoms include abrupt onset of fever, diffuse body aches, headache, malaise, nausea, vomiting, diarrhea, conjunctival suffusion, photophobia, and abdominal pain. Hemorrhagic rashes and bleeding manifestations may be seen in severe disease. Shock and resulting hypoperfusion leads to target organ failure, resulting in worse outcomes. Severe disease may see organ involvement like hepatitis, encephalitis, ALI/ARDS, pulmonary edema, diffuse alveolar hemorrhage, and meningitis. Dengue fever is identified with the help of characteristic plasma leakage which may lead to fluid accumulation in pleural and abdominal cavities. The case fatality rate may range from 50% in hantavirus pulmonary syndrome to <1% in dengue hemorrhagic fever.

Table 15.5 Samples that may be processed depends upon the viral infection and the organs involved

Viral infection	Samples that may be processed
Influenza	Nose swabs, throat swabs, nasopharyngeal aspirates, tracheal aspirates, bronchial washings
CMV	Blood, saliva, urine, other bodily fluids
HSV	BAL fluid

15.5 Investigations and Differential Diagnosis

Since viral infections have a very nonspecific presentation, a very high index of suspicion is required to consider a possible viral etiology among a wide list of differential diagnosis. This suspicion will need confirmation with the help of certain investigative modalities. Even among the available investigations, hematological, biochemical, and radiological modalities may have nonspecific findings. In this scenario, the targeted microbiological investigations (viral isolation, detection of the virus by PCR or antigen assays, viral serology, and/or viral cytopathic effects) hold the key to the final diagnosis of a viral etiology. It may be not enough to hold the virus responsible for the clinicopathological condition by its mere presence in the evaluated samples. The definitive evidence in favor of a causal association between the virus and the clinicopathological entity is the demonstration of "defining" cytopathic effects. However, this may not always be achievable in real life conditions.

Samples for targeted microbiological evaluation will depend upon the primary organ involved as highlighted in the following table (Table 15.5).

It is important to collect the appropriate samples in adequate amounts for processing, in order to achieve the best possible diagnostic returns. For instance, the sensitivity of the nasopharyngeal swabs and bronchoalveolar lavage (BAL) is better than the nasal swabs for detecting respiratory viruses. Hence, these methods may be preferred over the nasal swabs for diagnostic purposes.

We will now discuss each one of the microbiological methods with its advantages and limitations as follows

1. *Viral PCR assays*—This form of investigation is being considered as gold standard because it is rapid and highly sensitive to pick up minute viral nucleic acids in the appropriate clinical samples. This modality may be utilized to diagnose any of the viral infections. The highest sensitivity of PCR assay to diagnose influenza in upper respiratory tract (URT) samples is within 3 days from the beginning of symptoms. However, clinicians should remember that URT samples may be falsely negative in patients with established viral pneumonia, wherein evaluation of BAL may be preferred. RT-PCR detects CMV in blood samples after a median ICU stay of 12 days, with the highest viremia being detected after a median of 26 days in the ICU. The exact schedule of testing to

detect CMV reactivation remains to be ascertained for nonimmunocompromised patients as against a weekly assessment in immunocompromised. Adenovirus infection may be diagnosed by PCR assays of BAL, liver, fecal or CSF samples. However, in the absence of relevant symptoms, positive PCR assays of the respiratory secretions and fecal samples may signify viral shedding and not acute adenoviral infection. This modality remains the preferred diagnostic modality for avian influenza, RSV, parainfluenza virus, herpes simplex virus, human metapneumovirus, herpes zoster, and coronavirus also. Quantitative PCR analysis may also help in predicting prognosis as higher viral loads are related to higher mortality rates and declining viral loads on treatment underscores response to therapy. Higher viral loads will also favor the possibility of active infection rather than latent infection. The limitations of PCR assay include nonstandardization and higher cost of commercially available systems. It will also not help to differentiate latent from active infection.

2. *Viral antigen detection*—This method is advantageous over shell vial cultures because of its rapid turnover and higher sensitivity and specificity. Recognition of pp65 antigen from peripheral blood leukocytes utilizing monoclonal antibodies is one of the preferred diagnostic modalities for diagnosis of CMV infections. The consecutive samples may be interpreted for serial rise in CMV antigen titers to identify CMV reactivation as against latent infections. However, the sensitivity of this test requires sufficient leukocytes to be present in peripheral blood film. Detecting viral antigens is laborious and requires instant processing of samples. Apart from these limitations, this is a highly subjective test which requires rendition of an expert microscopist.
3. *Viral serological methods*—This methodology may be utilized to diagnose CMV and EBV infections. CMV infection encountered in ICU patients is mostly reactivation of an old infection rather than being a primary infection. In this scenario, an active CMV infection is confirmed with the demonstration of CMV specific IgM antibodies along with four fold increase of IgG titers in paired sera. Singular elevation of IgM titers may highlight a primary infection or a false positive test in presence of either a HHV6/EBV infection or rheumatoid factor positivity. Similarly, false negative tests may also occur in the presence of rheumatoid factor. Hence if the clinical presentation and serological tests for CMV are discordant, then rheumatoid factor, IgM EBV and IgM HHV 6 should be evaluated in order to rule out false positive and negative tests. EBV infections may be suspected in the presence of heterophile antibodies and/or EBV IgM antibodies.
4. *Viral isolation*—The virus may be isolated utilizing tissue culture or shell vial culture practices. It used to be considered as a gold standard before the advent of PCR assays. However, it has become obsolete now due to its low sensitivity and specificity. Besides, it is laborious and the results may take up to 14 days to become available. In particular, CMV viruria may signify primary infection or long-term asymptomatic virus shedders following a primary infection. Hence interpretation of CMV viruria requires a proper clinical assessment to rule out other differential diagnosis.

5. *Viral cytopathic effects*—The recognition of cytopathic effects in the viral culture supports a diagnosis of acute as against a latent viral infection. The CMV cytopathic effects include cytomegaly, intranuclear basophilic inclusions surrounded by a clear halo (giving them a typical appearance of an owl eye) and clusters of intracytoplasmic eosinophilic inclusions. The CMV cytopathic effects occur very slowly and may resemble HSV in first 1–2 days. The CMV culture needs to be observed twice a week to record typical cytopathic effects for at least 3 weeks before reporting it as negative. The nuclear and cytoplasmic inclusions are specific for HSV and CMV infections, respectively. This technique requires a skilled intensivist and a pathologist. Thus, PCR assays are preferred over this technique at present.

Apart from the targeted microbiological investigations, CSF analysis and chest X ray may also help in diagnosis making as explained below.

Chest X Ray The chest X ray may show abnormalities in patients involved with one of the respiratory viruses such as bilateral basilar patchy or interstitial infiltrates. These infiltrates usually subsides slowly over a period of 6 weeks. However, these abnormalities are nonspecific and are not peculiar for any of the viruses. Thus the chest X ray, at best, helps to exclude differential diagnosis such as typical or atypical bacterial pneumonias.

CSF The CSF may require evaluation in patients with clinical presentation suggestive of meningoencephalitis. The CSF is usually clear with a high lymphocytic white cell count, normal glucose levels and a normal to raised protein levels. Of note, lymphocytic pleocytosis is also noted in tubercular, fungal or partially treated meningitis. Polymorphonuclear leukocytes in CSF signifies bacterial meningitis, or these may also be found in early enteroviral, WNV, arboviral or CMV infections. Decreased CSF glucose levels are found in meningoencephalitis due to enterovirus, mumps, VZV, LCMV, and HSV. PCR assay of the CSF helps to determine the culprit virus after the first few days of illness.

Of note, other hematological and biochemical investigations are usually nonspecific and they do not help to make a diagnosis on their own. These may include relative lymphopenia or atypical lymphocytes, associated with other biochemical abnormalities such as mild elevation of serum transaminases in liver function tests. The atypical lymphocytes on the peripheral smear may help to recognize infectious mononucleosis like syndrome in CMV and EBV infections. Leukopenia, thrombocytopenia, deranged prothrombin time, and raised D-DIMER levels will support a diagnosis of viral hemorrhagic fever. Hemoconcentration and rising hematocrit levels are characteristically seen in dengue hemorrhagic fever. The hemorrhagic fevers can be diagnosed and the culprit virus identified, by subjecting the serum or any infected tissue to antigen detection by antigen capture ELISA, serology, RT-PCR or cell cultures as discussed above.

15.6 Management

Management of viral infections in ICU settings begins with infection control. Apart from universal infection control practices, care should be taken that open suction systems, endotracheal intubation, BiPaP, nebulizers, and ventilation systems do not spread infections in the critical care settings. Disinfection should be routinely employed as it is highly active against most of the viruses. Other infection control measures to control transmission by airborne droplets and by contact should be part of every ICUs routine practice. Isolation may be required in viral hemorrhagic fevers and influenza. Of note, isolation is recommended in avian influenza, even though the human to human transmission is not very common. Most of the viral infections require supportive management, however, specific therapies may be available for some of them.

15.6.1 Supportive Management in Viral Infections

15.6.1.1 Viral Infections of the Nervous System

Mostly these infections requires supportive therapy which includes management of cerebral edema, high intracranial pressure, hypoxemia, low cerebral perfusion pressure, fever, and seizures. These associated complications require urgent identification and management as they may worsen underlying neurological damage.

15.6.1.2 Viral Infections of the Respiratory System

The management is largely supportive and includes dealing with the associated complications. Many of the complications such as pneumonia, adult respiratory distress syndrome, asthma/COPD exacerbations, and restrictive lung disease due to Guillain–Barré syndrome may end as hypoxic and/or hypercapnic respiratory failure. This will require appropriate respiratory supportive management and ventilatory (invasive and noninvasive) strategies. In particular, management of ARDS will include protective ventilatory strategies such as prone positioning, low tidal volume, high PEEP, recruitment maneuvers, high frequency oscillation ventilatory strategy, and extracorporeal membrane oxygenation [ECMO]. Utilization of ECMO has improved outcomes and 60–70% of patients may survive to get discharged from hospital.

15.6.1.3 Viral Myocarditis

Severe cases may require mechanical ventricular assist device support, as a bridge therapy until patient improves or until transplantation is possible.

15.6.1.4 Viral Hemorrhagic Fever

Notification of these cases is a must to alert the local and national public health officials. Immediate isolation of the cases, even if suspect, is required for infection control and for preventing transmission. Significantly, no specific treatment modalities are available and so only supportive care is possible. *Corticosteroids should not be used.*

15.6.2 Specific Management of Viral Infections

The specific antiviral therapies may be needed, as soon after a diagnosis, in only a few handfuls of viral illnesses.

15.6.2.1 Specific Therapy for Respiratory Infections

(a) *Influenza* (H1N1/H5N1)—Out of neuraminidase inhibitors (NAI) and amantadine groups of antivirals, the latter are no longer preferred on account of high resistance to these drugs. Oseltamivir is indicated in severe infections or in areas endemic with strains having high mortality (e.g., H5N1). In these instances, antiviral therapy may be provided on clinical suspicion alone even without any laboratory confirmation. On the contrary, their use in nonsevere patients should be discouraged because of fear of production of resistant strains. If oseltamivir is instituted within 48 h of onset of illness, then it has a chance to reduce complications/disease severity along with illness duration. It is given in a dose of 75 mg twice daily for 5 days, which may be extended for 10 days in severe infections. Bioavailability of oseltamivir, administered through Ryles tube, in critically ill patients is comparable to that in uncomplicated H1N1 infected individuals. Higher doses of oseltamivir (150 mg twice a day for 10 days) may be used in seriously ill patients, influenza B strains, H5N1, resistant/reduced susceptibility strains of influenza A and infection at sites with reduced drug penetration (e.g., central nervous system). Even though, this regimen is safe and well tolerated, there is not much evidence in support of it. Besides, there are concerns regarding antiviral resistance with high dose oseltamivir. Treatment of oseltamivir resistant H5N1/H1N1 strains may be challenging. Intravenous zanamivir, inhaled laninamivir or combination antivirals such as oseltamivir-zanamivir and NAI-ribavirin-favipiravir may be utilized for treating resistant influenza. Low dose corticosteroids have been used in septic shock due to severe influenza and SARS/VZV pneumonitis so as to decrease the inflammatory tissue injuries. However, its use may lead to slower clearance of viral particles, increased rates of nosocomial infectious complications and mortality. Beneficial role of plasma and hyperimmune globulins in severe avian influenza (H5N1) and swine flu (H1N1) has been suggested by few case control studies and randomized controlled trials. However, the most potent intervention is to vaccinate the elderlies and the high risk individuals against seasonal influenza with the available vaccines.

(b) *RSV*—Aerosolized ribavirin is recommended only for immunosuppressed and children. Corticosteroids and immunotherapy may be combined along with ribavirin. Intramuscular palivizumab may be considered as prophylaxis in high risk patients.

(c) *Management of SARS-CoV-2*—The spectrum of illness secondary to SARS-CoV-2 ranges from a mild uncomplicated illness to severe pneumonia with ARDS with multiorgan failure and shock.

The treatment strategies are still evolving. The treatment of uncomplicated illness and mild pneumonia (without risk factors) is by enlarge supportive and

entails home isolation, symptomatic care, educating preventive measures and coming back to hospital if warning symptoms develop. Various antiviral agents are being used including hydroxychloroquine, remdesevir and convalescent plasma, beside others. It is important to initiate antiviral agents in moderate disease (RR > 24/min, SpO2 < 93%) rather than late in the course in severe disease. Oxygen support with face mask or HFNO should be given as per respiratory status and intubation to be done when it fails or work of breathing increases substantially. Anticoaugulation is to be given in moderate and severe disease in prophylactic and high prophylactic dose respectively. RECOVERY trial has shown substantial mortality benefits in patients on oxygen or mechanical ventilation. Immunomodulators like tocilizumab and itolizumab are being tried in the cytokine storm phase when the disease is worsening despite use of corticosteroids.

(d) *MERS-CoV*—Treatment is largely supportive with no specific antivirals. Animal studies support the use of ribavirin and interferon 2a; however, similar advantage has not been observed in small observational human studies.

(e) *VZV pneumonitis*—Acyclovir may be efficacious if utilized early in the course of infection.

(f) *Parainfluenza virus*—Aerosolized ribavirin for immunosuppressed patients only, not to be used in immunocompetent patients.

(g) *Human Metapneumovirus*—Treatment is largely supportive with no specific antivirals. Aerosolized ribavirin may be utilized only for immunosuppressed patients. The efficacy and safety of ribavirin in humans are not well established.

(h) *Adenovirus*—Treatment is largely supportive, with antivirals only for immunosuppressed patients and those with severe infections. Small case reports and non-randomized studies support the use of cidofovir in immunosuppressed patients. Immunosuppressed individuals may need preemptive cidofovir therapy based on weekly virological surveillance. Pooled IVIg may be used as complementary therapy as it has neutralizing antibodies against adenovirus. Ganciclovir and lipid ester derivatives of cidofovir are under evaluation for efficacy against adenovirus.

(i) *Rhinovirus*—Intranasal interferon (IFN) a-2b is useful for decreasing the symptoms and in primary prevention of rhinovirus infections. Further role in treatment of critically ill patients with severe rhinovirus infections is still not clear.

(j) *CMV*—The drugs available to treat CMV infections include ganciclovir, valganciclovir, acyclovir, valacyclovir, maribavir, foscarnet, and cidofovir. These drugs have been used prophylactically, preemptively or when the critically ill patients demonstrate CMV viremia. All these management strategies aim to start the therapy early so as to avoid development of end organ disease. Therapy is started universally in preventive strategy in comparison to preemptive therapy, where it is started only in high risk patients. The treatment should be started in immunosuppressed individuals, who may have severe manifestations of disease, and in patients with end organ involvement attributable to CMV infection. Severe CMV-CAP is one such example where treatment is required in immunocompromised patients or in severe pneumonia associated with hypoxemia in

immunocompetent patients. Important side effects of the antivirals used in managing CMV infections include bone marrow suppression and teratogenicity. Though there is enough evidence to not advise CMV therapy in immunocompetent patients, the experts feel that the same may not be held for critically ill immunocompetent patients. As against a complete course of antivirals in immunocompromised patients, only a limited duration of therapy may be required in immunocompetent patients just enough to bear the crisis of the acute phase. Pending convincing evidence, the experts advice that critically ill patients should be subjected to a clinical evaluation and those with high risk factors to acquire CMV infection should be offered treatment. Even though such an approach met with success in animal studies, only a handful of human studies have shown a decrease in rates of CMV infection and its sequelae. Well-designed trials are needed to draw conclusions on the role of periodic viral load monitoring to trigger antiviral therapy in critically ill immunocompetent patients. The dose of intravenous ganciclovir for CMV therapy is 5 mg/kg 12 hourly for the duration of infection. The oral equivalent of ganciclovir is valganciclovir which may be given for the entire duration with the same efficacy or may be started after the initial intravenous ganciclovir to complete the entire course of therapy. The dose of valganciclovir is 900 mg 12 hourly, to be given for 21 days. As discussed previously, immunocompetent individuals may not require the complete course as they may become better after receiving therapy for 1–2 weeks. The experts opine that the antiviral may be continued for an additional 1 week after the patient shows improvement in order to prevent a relapse. Foscarnet is an additional option, but it may not be preferred because of its nephrotoxicity. Foscarnet may be recommended in Ganciclovir resistant CMV.

(k) *HSV*—Acyclovir and valacyclovir have been used in patients with HSV related bronchopneumonitis or ARDS because of their good pulmonary bioavailability. However, the evidence of their safety and efficacy has been provided only by case reports or cohort studies. Studies have shown that even though acyclovir had the ability of restraining activation of herpes virus in ARDS patients, it did not have any additional benefit of decreasing duration of mechanical ventilation or mortality rates in immunocompetent patients with HSV bronchopneumonitis or ARDS.

(l) *Role of corticosteroids*—Corticosteroids have been used in influenza, SARS and VZV pneumonitis in order to decrease damage induced by inflammation in severe pneumonia. Dexamethasone is being currently used with evidence of benefit in COVID-19.

(m) *Role of immunotherapies*—Among the immunotherapies palivizumab, IVIg, plasma exchange and combination ganciclovir-CMV immunoglobulins have been approved for high risk pediatric RSV infection, influenza, GBS, and CMV pneumonitis, respectively.

15.6.2.2 Specific Therapy for EBV Reactivation

There are no specific therapies, corticosteroids may be considered in the presence of hemolysis, thrombocytopenia or significant neurological involvement.

15.6.2.3 Specific Therapy for ARDS

Management of ARDS is largely supportive with oxygen support, protective ventilatory strategies, broad spectrum antibiotics, and antibiotic coverage for atypical organisms forming the backbone of support. Specific therapies may have a role to play in certain viral etiologies. For instance, ganciclovir and oseltamivir have been considered for CMV related ARDS and influenza, respectively. No specific treatment is available for MERS and SARS, however, ribavirin has been utilized without much promising results. Acyclovir has been used in HSV related ARDS with no advantages in terms of improvement of respiratory failure, mortality or duration of ventilation when compared with controls. Even though there is no concrete supportive evidence for acyclovir, it may be advisable to consider it as a therapeutic option in ARDS patients with HSV tracheobronchitis.

15.6.2.4 Specific Therapy for Viral Encephalitis

High dose intravenous acyclovir for at least 2–3 weeks is the backbone of management for herpes and varicella encephalitis. Early administration of acyclovir reduces mortality and ensuing cognitive deficits. Longer duration of antivirals may be required in immunosuppressed patients. Combination of foscarnet and ganciclovir, foscarnet alone, and pleconaril (inhibitor of viral replication) are indicated in CMV, HHV6, and enteroviral encephalitis, respectively. Corticosteroid use is not routinely advocated and they should be utilized only if associated with cerebral edema such as in postinfectious encephalitis. Experts also advice to use steroids in VZV encephalitis in order to prevent inflammatory vasculopathy. Intravenous immunoglobulins or plasma exchange may be tried in the setting of postinfectious encephalitis after the failure of steroids.

15.6.2.5 Specific Therapy for Myocarditis

Corticosteroids have been used in certain studies, however, meta-analysis have found that the use is controversial as they do not reduce mortality. A systematic review after evaluating the available evidence concluded that intravenous immunoglobulin (IVIg) cannot be recommended in viral myocarditis.

15.6.2.6 Specific Therapy for Viral Hemorrhagic Fever

Management of viral hemorrhagic fever is largely supportive. The pillars of therapy are maintenance of intravascular volume and electrolytes with appropriate intravenous/oral fluids, management of hypotension with vasopressors/inotropes, management of bleeding with transfusion of appropriate blood products, and avoidance of medications like aspirin, nonsteroidal anti-inflammatory drugs and intramuscular injections. Secondary bacterial infections should be diagnosed at the earliest and managed with appropriate antimicrobials. Ribavirin is indicated to treat Crimean–Congo hemorrhagic fever with a bolus of 30 mg/kg followed by 15 mg/kg for 4 days and then 7.5 mg/kg for 6 days. Vaccination is effective against Kyasanur forest disease.

Suggested Readings

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Tuberculosis in Critical Care

16

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Key Points

- Tuberculosis (TB) uncommonly results in complications such as acute respiratory distress syndrome, septic shock, multiorgan dysfunction, and disseminated intravascular coagulation, which necessitate intensive care unit (ICU) admission.
- Mortality of TB patients requiring ICU care is high compared to other conditions.
- A high index of suspicion and timely initiation of TB treatment are key to improve survival.
- Treatment of TB in ICU patients could be complicated by impaired enteral absorption of drugs.
- Appropriate infection control measures are necessary to prevent airborne spread of TB infection from potentially infectious TB patients admitted to the ICU.

16.1 Introduction

Although tuberculosis (TB) figures among the top 10 causes of mortality globally, it is rather infrequently encountered in the intensive care unit (ICU) setting even in countries where TB is widely prevalent. Patients with TB constitute less than 2% of total ICU admissions (Muthu et al. 2018; Frame et al. 1987). Notwithstanding, these patients pose considerable challenges in terms of timely diagnosis, treatment, and

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Table 16.1 Common problems encountered in TB patients admitted to the ICU

Acute respiratory failure
– ARDS in miliary TB
– Tuberculous pneumonia
– Extensive parenchymal destruction by untreated pulmonary TB
– Massive hemoptysis with pulmonary aspiration
– Airway obstruction in laryngeal TB
Acute on chronic respiratory failure
– Destroyed lung with intercurrent problems such as bacterial pneumonia, hemoptysis, heart failure
TB meningitis with poor sensorium
– Hydrocephalus
– Increased intracranial pressure
– Vasculitic infarcts
– Hyponatremia (cerebral salt wasting, inappropriate antidiuretic hormone secretion)
– Status epilepticus
TB pericardial effusion with cardiac tamponade
Intestinal obstruction/perforation peritonitis
Septic shock/multiorgan dysfunction syndrome
Disseminated intravascular coagulation
Hemophagocytic lymphohistiocytosis
Acute adrenal insufficiency
Serious adverse drug reactions
– Acute liver failure
– Acute renal failure
– Stevens-Johnson syndrome/toxic epidermal necrolysis

infection control. Patients with clinically severe forms of TB may require admission to the ICU. Studies from various settings indicate that a broad range of 1–25% of patients with active TB require ICU admission (Patel et al. 2017; Tsai et al. 2008; Levy et al. 1987; Lui et al. 2014; Eveloff et al. 1994; Rao et al. 1998; Silva et al. 2010). The most common reason for transferring a patient with active TB to the ICU is acute respiratory failure (ARF) (Muthu et al. 2018; Frame et al. 1987; Zahar et al. 2001; Valade et al. 2012). Other common indications include mycobacterial septic shock and multiorgan dysfunction syndrome (MODS). However, in some settings, TB meningitis is the most common reason for ICU admission among TB patients. About 40% of patients with TB meningitis would have concomitant pulmonary disease. Less common indications could be massive hemoptysis, pericardial effusion causing cardiac tamponade, Addisonian crisis, airway obstruction in laryngeal TB, disseminated intravascular coagulation (DIC), and seizures caused by tuberculomas in the brain. Importantly, TB patients may also experience acute liver failure due to hepatotoxic drugs and rarely acute renal failure, mainly rifampicin-induced (Hagan and Nathani 2013) (Table 16.1).

These are all settings when a patient already diagnosed with TB or else an obvious possibility of TB (such as chronic meningitis, cardiac tamponade) is shifted to the ICU. The most challenging situation, however, is when patients are admitted to the

ICU with one or more organ dysfunctions such as ARF or MODS, but without any obvious suggestion of TB as the underlying cause. In Taiwan, 4% of patients with culture-confirmed pulmonary TB over the period 2005–2010 presented with clinical and radiographic manifestations similar to severe community-acquired pneumonia that required ICU admission (Tseng et al. 2012). In a study from Hong Kong, 48 of 349 patients with TB admitted to the hospital over a 2-year period died. In about 50% patients (23 of 48) that died by Day 90, a diagnosis of TB was not made antemortem (Lui et al. 2014). In a study on burden of TB done at four South African ICUs, 7 (15%) of 46 patients with confirmed TB died before the diagnosis was made (Calligaro et al. 2015). Possibility of TB was not considered at the time of ICU admission in about 13% of patients with TB admitted to the respiratory ICU of a large teaching hospital in northern India (Muthu et al. 2018). Thus, a diagnosis of TB is missed in a considerable proportion of patients admitted to ICUs across different settings. In a multicentric study involving 34 ICUs in India, of the 456 patients admitted with fever of less than 2 weeks duration and one or more organ dysfunctions, no patient received a diagnosis of TB (Singhi et al. 2017). Notably, a specific etiological diagnosis could not be achieved in about 20% of patients. Hospital mortality was considerably higher in these patients (27% vs 15%) compared to the rest, in whom the most common diagnoses were dengue, scrub typhus, meningoencephalitis, sepsis, pneumonia, and leptospirosis. It is possible that at least some of the patients without a specific diagnosis could have had TB that was not diagnosed antemortem.

Pulmonary TB might be incidentally detected on routinely performed chest radiographs in patients admitted to the ICU for other indications such as alcoholic liver disease, chronic kidney disease, and diabetes complications. Likewise, in endemic countries, it is not uncommon for thrombolysis or anticoagulation for the treatment of acute coronary syndromes to result in hemoptysis, unmasking paucisymptomatic or healed pulmonary TB lesions. Further, patients with active TB could be admitted to the ICU with unrelated illnesses like trauma, emergency surgeries, or organ failures.

16.2 Acute Respiratory Failure in TB

Notwithstanding the fact that TB most commonly affects the lungs, often extensively, ARF is an infrequent complication of pulmonary TB. Incidence of ARF among patients with active TB admitted in non-ICU inpatient settings is about 1.5% (Levy et al. 1987; Agarwal et al. 1977). On the other hand, almost 80% patients with TB admitted in the ICU have ARF (Frame et al. 1987; Eveloff et al. 1994; Erbes et al. 2006). Patients with TB could develop ARF by several mechanisms. First, patients with extensive parenchymal destruction from untreated or previously treated pulmonary TB could develop ARF as a complication. Second, miliary TB might be complicated by acute lung injury leading to acute respiratory distress syndrome (ARDS) (Fig. 16.1). Miliary TB is particularly associated with a high risk of ARDS. In a large case series from northern India, about 15% of patients with miliary TB developed ARDS (Sharma et al. 2006).

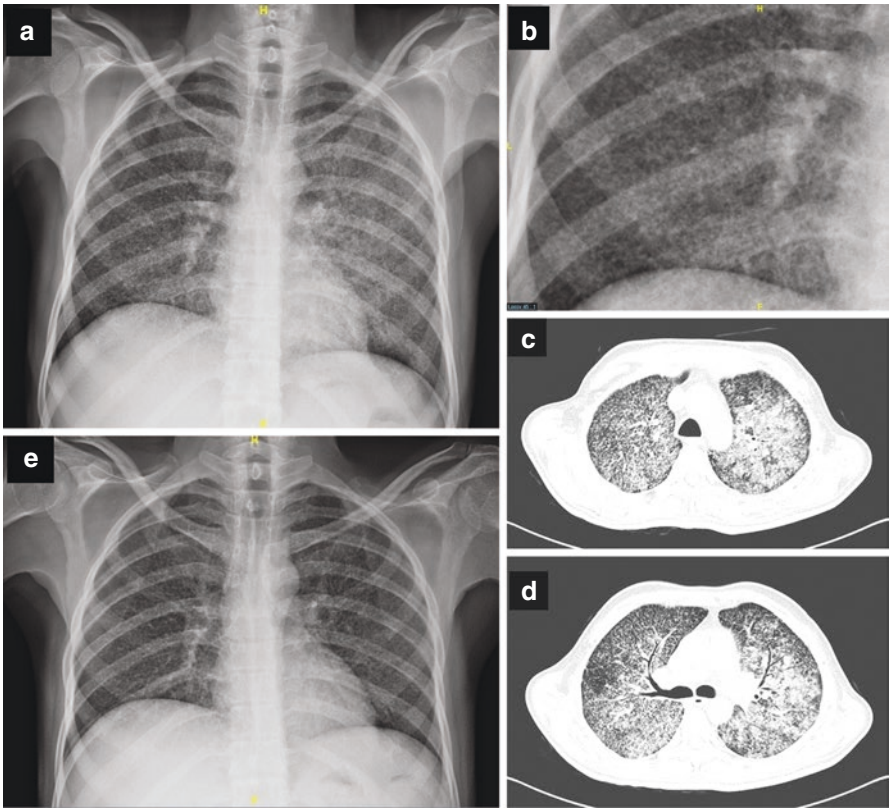

Fig. 16.1 Acute lung injury in miliary TB. A 40-year-old, HIV-negative man presented with fever for 2 months and breathlessness for 10 days. He was tachypneic (respiratory rate 44/min) and his oxygen saturation on room air was 87%. The chest radiograph showed diffuse miliary mottling (Panel **a**; magnified view of right lower zone in Panel **b**), and a thin-veil of haziness particularly over the left lung fields (Panel **a**). High-resolution computed tomographic images (Panels **c**, **d**) showed patchy areas of consolidation and ground-glass opacities in a background of randomly distributed micronodules. The patient had clinical and radiographic improvement at 2 weeks (Panel **e**) following treatment with supplemental oxygen, anti-TB treatment, and adjunctive steroids

Third, primary tuberculous pneumonia, characterized by parenchymal consolidation with or without endobronchial spread, in itself could result in ARF necessitating mechanical ventilation (Fig. 16.2) (Kim et al. 2008). This presentation is difficult to differentiate from bacterial pneumonia, the only difference being the longer duration of symptoms before presentation in patients with tuberculous pneumonia as compared to bacterial pneumonia. A high index of clinical suspicion is required in such a situation. Of the 115 patients with ARF caused by TB treated at a South Korean ICU over an 18-year period, ARF was attributable to extensive parenchymal damage by previous episodes of TB in 25 patients (Kim et al. 2008). Of the remainder, 66 patients had tuberculous pneumonia and 24 had miliary TB. Of the

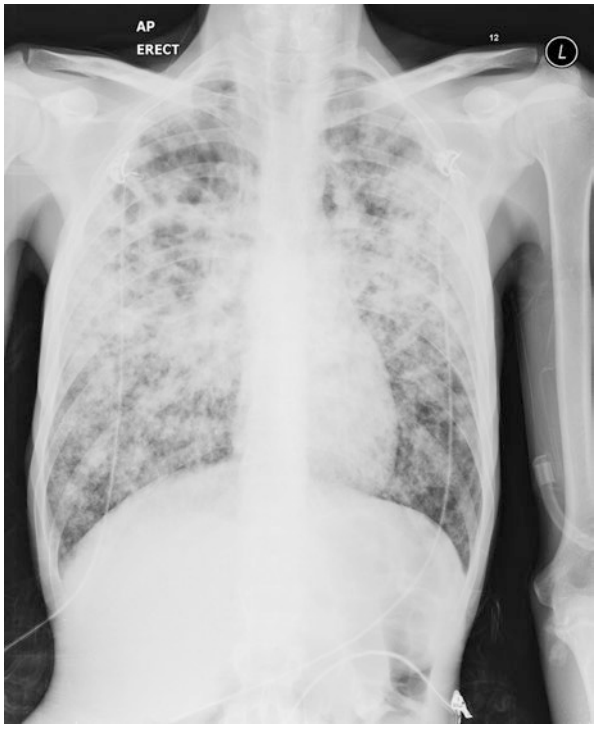

Fig. 16.2 Tuberculous pneumonia. Chest radiograph of a man with active pulmonary TB who presented with type 1 respiratory failure. There is a cavitatory lesion in the right upper zone and extensive bilateral nodular infiltrates larger than miliary micronodules, which are typically 1–2 mm in size. (Reproduced from: Hagan G, Nathani N. Clinical review: Tuberculosis on the intensive care unit. Crit Care. 2013;17:240. ©BioMed Central Ltd. Licensed under CC BY 4.0)

469 patients with ARDS treated over a 16-year period at a teaching hospital in northern India, 18 patients had TB-related ARDS; only six of them had miliary TB (Muthu et al. 2017). It is possible that the rest actually had tuberculous pneumonia.

Fourth, massive hemoptysis with pulmonary aspiration could also lead to ARF in patients with TB. Finally, in human immunodeficiency virus (HIV)-infected and immunosuppressed patients, TB might uncommonly co-exist with other opportunistic infections such as pneumocystis pneumonia and disseminated cytomegalovirus disease. Nearly two-thirds of TB patients with ARF would satisfy the consensus diagnostic criteria for ARDS, and about a third would have concomitant organ dysfunctions in the form of septic shock, DIC, and multiorgan failure (Sharma et al. 2006; Kim et al. 2008; Muthu et al. 2017).

Clinically these patients present with typical features of pulmonary TB like fever, cough, and weight loss (Deng et al. 2012). Presence of dyspnea could indicate the development of ARDS (Sharma et al. 2006). Of note, hemoptysis is uncommon among TB patients developing ARDS. Duration of symptoms could vary from days to months (Levy et al. 1987). Patients with miliary TB are more predisposed to sudden development of ARF, especially when the diagnosis is delayed by >30 days (Sharma et al. 2006). In a study of 146 HIV-negative patients with pulmonary TB admitted to the ICU of a specialist TB hospital in Iran, the most common finding on computed tomography was ARDS-like bilateral infiltrates (17%), followed by parenchymal nodules (1–2 cm size; 14%), cavitation (11%), consolidation (10%),

interstitial involvement (9%), ground-glass opacities (7%), pleural effusion or thickening (7%), and miliary nodules (2%). Enlarged lymph nodes were present in about 40% of adults (Hashemian et al. 2015).

Histopathology of the lungs in TB-ARDS may show evidence of widespread parenchymal involvement with caseation necrosis, interstitial granulomatous inflammation, small vessel microthrombi, congestion, edema, and diffuse hyaline membranes (Murray et al. 1978). However, evidence of diffuse alveolar damage in the form of hyaline membrane formation may not be present in all cases of TB-ARDS. Some cases show features of confluent TB bronchopneumonia only (Levy et al. 1987).

16.3 TB Meningitis

Patients with TB meningitis often require endotracheal intubation for airway protection or when the respiratory efforts are poor. The most important determinant of survival in patients with TB meningitis is the stage of TB meningitis, which is largely determined by the Glasgow Coma Scale score. Several factors contribute to impairment of sensorium in TB meningitis. They are, communicating and at times obstructive hydrocephalus, elevated intracranial pressure, vasculitic infarcts, and hyponatremia. The latter is seen in about 40% of patients. Most of these patients have hypotonic hyponatremia, the cause of which could be either syndrome of inappropriate antidiuretic hormone secretion (SIADH) or cerebral salt wasting syndrome. Differentiating these two opposing conditions is often challenging, the only distinction being intravascular volume status, assessment of which could prove difficult in critically-ill patients. Some investigators have reported that cerebral salt wasting is more common than SIADH in patients with TB meningitis (Misra et al. 2016), and that volume depletion caused by salt wasting might contribute to strokes (Misra et al. 2018). Application of high positive end-expiratory pressure (PEEP) levels to maintain oxygenation could potentially decrease cerebral perfusion in patients with TB-ARDS and concomitant meningitis. However, the effect of high PEEP on intracranial pressure may not be clinically significant (Boone et al. 2017).

16.4 Septic Shock and Multiorgan Dysfunction in TB

Rarely, a clinical syndrome characterized by shock and multiorgan dysfunction, mimicking septic shock caused by gram-negative infections, has been described in TB (Pène et al. 2001). Presence of vasodilatory shock characterized by a high cardiac output and decreased systemic vascular resistance in these patients along with renal failure, ARDS, and DIC closely resembles gram-negative sepsis (Ahuja et al. 1992). Adrenal involvement was unlikely to explain these findings. Although a rapidly fatal form of TB was well known in the pre-chemotherapy era, advent of the HIV epidemic brought back this form of TB to attention (Gachot et al. 1990). Apart from HIV infection, such a presentation has been reported in other immunosuppressed conditions, advanced age, alcohol abuse, malignancy, diabetes, renal

failure, and pregnancy (Jog et al. 2011). *Mycobacterium tuberculosis* is an important cause of blood stream infection and severe sepsis in HIV-infected patients from sub-Saharan Africa (Cummings and O'Donnell 2015). In the tri-national Cooperative Antimicrobial Therapy of Septic Shock (CATSS) database, 53 patients with TB septic shock, defined as confirmed *M. tuberculosis* infection and hypotension requiring vasopressors in the absence of other pathogens, were identified over a 12-year period (Kethireddy et al. 2013). As compared to other bacterial septic shock, patients with TB septic shock were younger and malnourished, often with normal white cell counts despite overt clinical signs of infection; >90% had respiratory involvement—multilobar consolidation, miliary mottling, occasional nodules, and cavitation were the radiographic findings; and 55% had extrapulmonary involvement (Kethireddy et al. 2013). Although most of these patients had underlying conditions such as diabetes, alcohol/substance abuse, and immunosuppression including HIV infection, the frequency of these conditions was similar to the other septic shock patients. Only 20% of patients with TB septic shock survived to hospital discharge. Historical terminologies such as "sepsis tuberculosa gravissima," "sepsis tuberculosa acutissima," and "generalized non-reactive tuberculosis" are often used in contemporary literature to describe such a clinical course of TB. Sometimes this condition is also called Landouzy sepsis, which we think is inaccurate (Landouzy 1908). On post-mortem examination, many organs contain small necrotic foci surrounded by normal parenchymal cells, with very little inflammatory response; these lesions are, however, studded with innumerous TB bacilli (Arends 1950; O'Brien 1954).

16.5 Disseminated Intravascular Coagulation in TB

Like septic shock, DIC also could be encountered in patients with TB, albeit infrequently (Pène et al. 2001; Goldfine et al. 1969; Mavligit et al. 1972). In experimental studies, *M. tuberculosis* infection induces expression of tissue factor in macrophages (Kothari et al. 2012), which might explain the occurrence of DIC in patients with disseminated/miliary TB. In a large series of 833 patients with culture-proven TB, 27 (3%) patients had laboratory evidence of DIC; 16 patients had overt DIC with bleeding manifestations, most commonly upper gastrointestinal bleeding; 3 patients had arterial thrombosis in distal extremities (Wang et al. 2005). Nearly half of the patients with DIC also had ARDS and septic shock, and about two-thirds of patients with DIC died. In a study of hospitalized patients with HIV-TB, 29 (64%) of 45 patients had DIC (Janssen et al. 2017). Of the 128 patients with DIC diagnosed over a 1-year period at a South African hospital, 28 patients had TB; all of them had HIV co-infection (Mayne et al. 2018). All these findings suggest that DIC is fairly common among seriously-ill TB patients, and presence of DIC should not be considered a pointer against a diagnosis of TB. Very rarely, a triad of acute renal failure, autoimmune hemolysis, and DIC has been observed in patients with rifampicin hypersensitivity (Ip et al. 1991; Costiniuk et al. 2011). Rifampicin, particularly when used intermittently, could result in renal failure by other mechanisms also (De Vriese et al. 1998).

16.6 Hemophagocytic Lymphohistiocytosis in TB

TB is a relatively common cause of secondary hemophagocytic lymphohistiocytosis (HLH) in endemic countries (Brastianos et al. 2006; Chen et al. 2017). Till date, more than 70 cases of TB-associated HLH have been reported (Padhi et al. 2015). This, however, does not reflect the true magnitude of the problem. Presence of cytopenias and jaundice should arouse the possibility of HLH in patients with TB. Hemophagocytosis in the bone marrow and elevated serum ferritin levels are common as isolated findings in patients with TB (Visser and van de Vyver 2011). However, further evidence of cytopenias and organ dysfunction is required to make a diagnosis of HLH. Bone marrow examination demonstrates histiocytosis and hemophagocytosis in more than 90% of cases, but not invariably. Most of these patients were treated with adjunctive immunosuppressive treatment in addition to anti-TB treatment (Brastianos et al. 2006; Padhi et al. 2015). Despite early diagnosis and appropriate treatment, TB-HLH is associated with a mortality of about 50%.

16.7 When to Suspect TB in ICU Patients

A diagnostic possibility of TB should be considered in patients admitted to the ICU with severe pneumonia and underlying risk factors for TB such as old age, alcoholism, chronic renal failure, diabetes, HIV infection, and a history of immunosuppressive medications. In the absence of any of these predisposing factors, one should also consider a possibility of TB if the presenting illness is sub-acute. Duration of symptoms >1–2 weeks, white cell counts <12,000/μL, nodular/cavitating infiltrates, and upper lobe involvement are predictive of pulmonary TB among patients presenting as community-acquired pneumonia (Liam et al. 2006; Chon et al. 2013). Lower than expected levels of serum C-reactive protein and procalcitonin could be indicative of TB as the etiology (Kang et al. 2009; Ugajin et al. 2011). TB should be considered among the differentials in patients with MODS of unclear etiology particularly when the preceding illness is sub-acute. Identifying miliary TB in patients presenting with ARDS is very challenging. Careful reading of the chest radiograph for the presence of miliary nodules is required. Presence of cytopenias and elevated serum alkaline phosphatase levels should heighten the suspicion. When doubtful, high-resolution computed tomographic imaging of chest should be performed. One needs to be mindful of the potentially destabilizing effect of shifting a patient requiring high PEEP settings for CT imaging.

In a seminal study, Eveloff et al. retrospectively analyzed the hospital charts of 14 patients with culture-confirmed TB, who were admitted to the ICU in a low-prevalence setting, to determine the reasons for diagnostic delay (Eveloff et al. 1994). The time to diagnosis ranged from 3 days to 3 months, and in 5 patients the diagnosis of TB was established only post-mortem. They concluded that

- Diagnostic delay was not due to a failure to consider the possibility of TB. In fact, adequate attempts were made to diagnose TB after sputum specimens were found to be negative for acid-fast organisms.

- However, most invasive diagnostic procedures such as bronchoscopy and bone marrow examination were negative for acid-fast organisms.
- Often co-existent bacterial infections acted as confounders, making clinicians believe that clinical worsening was due to bacterial sepsis rather than TB.
- Chest radiographs were often misinterpreted since typical findings of reactivation TB were seldom encountered.

This study was conducted before the advent of Xpert MTB/RIF assay, which is more sensitive and rapid than smear microscopy. To what extent this diagnostic delay could be improved by Xpert MTB/RIF testing is a matter of conjecture. In a randomized evaluation done in South Africa (Calligaro et al. 2015), Xpert MTB/RIF testing on tracheal aspirate samples of mechanically ventilated adults with suspected pulmonary TB had much better sensitivity than concentrated fluorescent smear microscopy for diagnosing culture-confirmed TB. This translated into faster treatment initiation at 48 h (92% vs 53%). However, there was no appreciable effect on mortality. About 30% of Xpert MTB/RIF-positive samples were negative by culture. At present, it is unclear whether these discordant results are false- or true-positives (Calligaro et al. 2015).

16.8 Treatment

The general principles of chemotherapy of TB apply to critically-ill patients as well. Since a delay in treatment initiation could adversely impact survival in critically-ill patients with TB (Lui et al. 2014; Zahar et al. 2001; Calligaro et al. 2015; Deng et al. 2012), clinicians should consider initiating presumptive treatment based on imaging findings alone, pending microbiological and/or tissue confirmation of diagnosis. However, critical illness per se may not be a valid indication for adding second-line drugs to presumptively treat TB. Standard combination of four first-line drugs should be sufficient in situations where drug-resistant TB is unlikely. The recently published first-ever national level survey of drug-resistance in India indicates that frequency of multidrug-resistant TB is quite uncommon (2.8%) among patients without a prior history of TB treatment, while it is 11.6% among previously treated patients (Ministry of Health and Family Welfare, India 2014–16). We do not recommend routinely adding second-line drugs to presumptively treat TB in the ICU setting. A history of TB treatment in the past and appropriate use of rapid diagnostic tests such as XpertMTB/RIF could help decide whether to add second-line agents or not (Calligaro et al. 2015).

On the other hand, while standard first-line drugs are sufficient in terms of coverage, one needs to bear in mind that the absorption, distribution, and elimination of most antimicrobials are considerably altered in a critically-ill patient (Shah et al. 2015). Anti-TB drugs are no exception. Typically, TB drugs are administered in ICU patients through a nasogastric tube after crushing the tablets. Enteral absorption is likely to get affected in the presence of circulatory shock, and enteral route may not be feasible in patients with intestinal obstruction or peritonitis caused by TB. While the pharmacokinetics of anti-TB drugs have been reasonably well

studied in healthy persons and those with active TB, very little data is available on the pharmacokinetics of first-line TB drugs in critically-ill patients. In a small study from South Africa (Koegelenberg et al. 2013), of 10 adult ICU patients administered TB drugs via enteral route, the maximum plasma concentration (C_{max}) was below the therapeutic level in 6 patients for rifampicin, 3 patients for ethambutol, and 2 patients for isoniazid; all had adequate plasma concentrations of pyrazinamide. Thus, in an ideal setting, anti-TB drugs should be administered via parenteral route in critically-ill patients. However, injectable preparations of isoniazid and rifampicin are not widely available. Hence, some experts suggest that "local regimens of alternative intravenous anti-TB drugs (e.g. a combination of intravenous rifampicin, moxifloxacin and amikacin) may be useful and effective to bridge the period of impaired gastrointestinal function." (Otu et al. 2018).

Notably, in a study of 77 patients with severe tuberculous pneumonia requiring admission to a Taiwanese ICU, empirical use of fluoroquinolones before the diagnosis of TB was associated with improved survival (Tseng et al. 2012). If injectable rifampicin is unavailable and the likelihood of TB diagnosis is high, one could consider using injection linezolid in lieu of rifampicin in seriously-ill patients until the time gastrointestinal tract function is restored. Linezolid has good bactericidal and sterilizing activity in TB. Other antibiotics commonly used in clinical practice such as meropenem and amoxicillin-clavulanic acid also have some useful antimycobacterial activity (Caminero et al. 2017).

The other question to be addressed is whether use of corticosteroids could help improve the outcomes in critically-ill TB patients. Patients with TB meningitis and possibly those with TB pericardial effusion experience a survival benefit from adjunctive steroid treatment (Prasad et al. 2016; Wiysonge et al. 2017). Reliable evidence from controlled clinical trials to inform the use of steroids in other forms of TB including those with ARF/ARDS, septic shock, and MODS caused by TB is lacking. Notwithstanding, one cannot rule out a beneficial effect in these groups of patients. Given this, the best possible solution would be to reconcile the observational evidence available on this group of patients with the larger body of trial evidence available on similar clinical conditions and arrive at an informed decision.

Of the 55 patients with miliary TB admitted during 1954–1978 at a Chinese hospital, 5 (18%) of 28 patients treated with chemotherapy alone died as compared to 2 (7.4%) of 27 patients treated with a combination of chemotherapy and prednisone (10 mg QID for Week 1, 20 mg OD Weeks 2–7, tapered off weekly over 3–5 months) (Sun et al. 1981). The difference in mortality could not be explained by a difference in meningeal involvement. Of the 14 patients with meningitis, 9 received prednisone—2 of them died; and 5 did not receive prednisone—1 of them died. Most of these patients were treated with a combination of isoniazid, para-aminosalicylic acid, and streptomycin; a few of them had received ethambutol or rifampicin. On the other hand, among children with miliary TB treated with HRZE/Eth at a South African hospital, 6 (14%) of 43 patients given prednisolone (2 mg/kg/day for 1 month, tapered off over the next month) died, whereas 7 (14%) of 51 patients who did not receive adjunctive steroids died (Hussey et al. 1991). Thus, it

is unclear whether routine use of steroids in miliary TB in the absence of meningeal disease is beneficial in patients receiving HRZE combination chemotherapy.

In a systematic review on the effect of steroids in pulmonary TB, the radiological and clinical improvement was faster with the use of steroids (Smego and Ahmed 2003). However, rifampicin-based chemotherapy was used in only 2 of the 11 trials included in this review. The incremental benefit of steroids in pulmonary TB as an adjunct to the present-day HRZE regimen is unclear (Critchley et al. 2014). Nonetheless, anecdotal evidence suggests that steroids might improve clinical outcomes in patients with TB-related ARF. In a study from South Korea (Kim et al. 2008), among patients with ARF caused by tuberculous pneumonia, the mortality was 57% among 30 patients treated with steroids as compared to 78% among 36 patients who were not treated with steroids. In an extended cohort of patients from the same center (Yang et al. 2016), unadjusted 90-day mortality did not differ by steroid use in 124 patients who had pulmonary TB with ARF, including 33 patients with miliary TB. However, adjunctive steroid use was associated with a lower odds of death on propensity score adjusted analysis. Further, use of steroids was associated with an increased risk of nosocomial infections mostly pneumonia. On the other hand, ICUs with a policy of not using steroids have reported a lower mortality of 28% in patients with TB-ARDS (Muthu et al. 2017). However, most probable reason for this lower mortality was that the patients were much younger compared to previous studies which have reported a high mortality, often in excess of 50% (Erbes et al. 2006; Deng et al. 2012; Yang et al. 2016; Duro et al. 2017).

The benefit of routine use of steroids in patients with ARDS (not TB-related) is a matter of disagreement and debate, with some evidence to suggest that early use might be beneficial (Bein et al. 2016; Thompson and Ranieri 2016; Seam and Suffredini 2016; Meduri et al. 2016). On the other hand, there is some evidence for modest mortality benefit when steroids are used in hospitalized patients with community-acquired pneumonia (Siemieniuk et al. 2015). As stated earlier, while it is widely known that adjunctive steroids are beneficial in TB meningitis and possibly pericarditis, a meta-analysis indicated that steroids might confer a mortality benefit irrespective of the organ affected by TB and whether rifampicin-based regimen is used or not (Critchley et al. 2013). In the face of this uncertainty, clinicians might consider using steroids in patients with TB-related ARF provided there are no contraindications and drug-resistant TB is unlikely.

Ventilatory management of ARF/ARDS in TB is no different from that caused by other etiologies. These patients are managed according to the standard ARDSnet mechanical ventilation protocol. The initial severity of hypoxemia, static lung compliance, and other physiological parameters such as PEEP and $P_{plateau}$ in patients with TB-ARDS were found to be similar to non-TB patients with ARDS (Muthu et al. 2017). The time-trends in lung mechanics were also similar. Non-invasive ventilation, if effective, could obviate the need for endotracheal intubation in carefully selected patients (Agarwal et al. 2005; Utsugi et al. 2006). While there are only a few reports of successful use of NIV in TB-related ARDS, handful of large case series suggest that NIV could be effective in acute exacerbations of chronic

respiratory failure in patients with pulmonary TB sequelae (Esquinas et al. 2014). Extracorporeal membrane oxygenation (ECMO) has been successfully used in TB-ARF patients with refractory hypoxemia (Omote et al. 2016). Sivelestat sodium is an inhibitor of human neutrophil elastase approved for clinical use in Japan and the Republic of Korea. Utsugi et al. had described the successful use of sivelestat in an elderly patient with confirmed miliary TB and ARDS (Utsugi et al. 2006). However, subsequent reports were not encouraging. In a meta-analysis of six randomized trials, sivelestat did not improve the survival in patients with ARDS due to other causes (Pu et al. 2017).

16.9 Prognosis of TB Patients Requiring ICU Admission

Patients with TB-ARF often require mechanical ventilation for prolonged periods. A few studies indicate that TB-ARF is associated with a high mortality of up to 88% when compared to other causes of ARF (Levy et al. 1987; Mansoura et al. 2014; Piqueras et al. 1987). However, some studies do indicate that mortality due to TB-ARDS is not worse as compared to other causes of ARDS (Muthu et al. 2017; Penner et al. 1995). Factors like underlying destroyed lung, higher APACHE II/SOFA scores on admission, hyponatremia, lower PaO_2/FiO_2 ratio, advanced age, and sepsis have been identified as risk factors for mortality (Sharma et al. 2006; Kim et al. 2008; Ryu et al. 2007; Lin et al. 2009). In a study of 85 miliary TB patients with ARDS from China, a shorter time to diagnosis, time from diagnosis to mechanical ventilation, and time to initiation of TB treatment were associated with survival (Deng et al. 2012). Complications which may be anticipated in mechanically ventilated TB patients include ventilator-associated pneumonia, pulmonary hemorrhage, pleural effusion or empyema and pneumothorax (Otu et al. 2018). A small study from Germany found that ICU-acquired complications like sepsis, nosocomial pneumonia, and acute renal failure contribute to mortality in TB patients admitted to the ICU (Erbes et al. 2006). Pneumothorax was observed in 14% of patients. It appears that pneumothoraces are common in TB patients receiving mechanical ventilation.

16.10 Recent Advances

Latent infections such as cytomegalovirus and herpes simplex virus are known to get reactivated in critically-ill patients (Walton et al. 2014). It has been recently suggested that reactivation of latent TB infection might occur in critically-ill patients as a result of stress and immunosuppression (Otu et al. 2018). However, no data exist to confirm or refute such a possibility. Of note, in a study from Taiwan, more than half of the ICU patients had indeterminate interferon-gamma release assay (IGRA) results due to a low mitogen response (Huang et al. 2016). Such indeterminate IGRA results were seen among patients with more severe illness.

16.11 TB Infection Control in the ICU

TB is spread by airborne droplet nuclei. Patients with active pulmonary TB admitted to ICU could transmit the infection to healthcare workers and visitors. ICU environments typically lack natural cross ventilation and are hotspots for nosocomial TB transmission. Moreover, aerosol generating procedures are frequently performed in the ICU setting, increasing the risk of TB transmission. Under ideal circumstances, patients with presumed or diagnosed infectious TB disease should be placed in an airborne infection isolation room constantly maintained at a negative pressure of at least 0.01 in. water gauge (2 Pa) lower than its surroundings with at least 12 air changes per hour, and the exhaust air from these rooms should not be recirculated or else done so only after HEPA filtration (Jensen et al. 2005). Unfortunately, such isolation rooms are seldom available in most resource-limited settings where TB is prevalent. In such situations, every attempt should be made to house the patient in a single room with sufficient natural ventilation and facilities for appropriate life support. In intubated patients, bacterial or heat and moisture exchange (HME) filters, capable of filtering particles of 0.3 μm size with an efficiency of >95%, should be placed on the expiratory limb of the breathing circuits and periodically replaced (Jensen et al. 2005). All persons entering the isolation room should wear at least a properly fitting disposable N95 respirator. For infection control purposes, a patient with TB is considered infectious for up to 14 days of effective TB treatment (Jensen et al. 2005).

Endotracheal intubation of TB patients carries a high risk of exposure to infectious aerosols. Likewise, aerosols are likely to be generated during airway suctioning, non-invasive ventilation, high-frequency oscillatory ventilation, tracheostomy, chest physiotherapy, nebulizer treatment, sputum induction, and bronchoscopy (Canadian Agency for Drugs and Technologies in Health 2011). A recent study on aerosol production during such medical procedures, however, did not support this notion (Li et al. 2017). The findings of this study should be interpreted with caution, and should not change current infection control practices.

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HIV in ICU

17

Pranav Ish and Neeraj Nischal

17.1 Introduction

With the advent of highly active antiretroviral treatment (HAART), screening for opportunistic infections and appropriate treatment for the same, there has been a trend to increased chronicity of HIV infection. Thus, there is an increased exposure of patients to intensive care units (ICU) due to prolonged survival. In the modern era of highly active antiretroviral therapy, clinicians must be aware of traditional opportunistic infections, as well as newer syndromes such as immune reconstitution inflammatory syndrome (IRIS), multicentric Castleman's disease, and primary body cavity lymphoma. They must recognize the drug toxicities and drug interactions. This chapter aims to address the above issues with a glimpse of the road ahead.

17.2 Epidemiology

As per estimates, 37.9 million people are living with HIV in 2018. Approximately two-thirds are living in Africa and 10% each in Americas and South-East Asia. Estimates of new infections reported was 1.7 million in 2018 with maximum contribution again from Africa. The number of deaths attributed to HIV/AIDS was 0.77 million. It is noteworthy that the majority of patients, new infections and deaths are all reported from resource-limited settings.

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Two major classification systems on HIV diseases are currently in use: the U.S. Centers for Disease Control and Prevention (CDC) (Centers for Disease Control and Prevention 1992) classification system, which assesses the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions. The definition of AIDS includes all HIV-infected individuals with CD4 counts of <200 cells/μL (or CD4 percentage <14%) as well as those with certain HIV-related conditions and symptoms. The alternate classification being the World Health Organization (WHO) Clinical Staging and Disease Classification System (World Health Organization 2007), which is based on clinical manifestations that can be recognized and treated by clinicians in diverse settings, including resource-constrained settings without access to CD4 cell count measurements or other diagnostic and laboratory testing methods.

Since the introduction of more potent antiretroviral agents in the mid-1990s, it has been apparent to all clinicians that the frequency of opportunistic infections has declined, and patient survival has increased (Palella et al. 1998). The decline in opportunistic infections has been uniform but, some neoplastic complications have not been affected in the same manner (Clifford et al. 2005; Cooksley et al. 1999; Grulich et al. 1999; Mocroft et al. 2004; Parker et al. 1998; Scadden 2003). Although Kaposi's sarcoma and primary central nervous system (CNS) lymphoma have declined in incidence, the incidence of non-primary CNS B-cell lymphoma has been stable, and may be increasing in terms of lifetime risk as patients live longer. In addition, it is becoming apparent that unusual tumors linked to human herpes virus 8 (HHV-8) are increasing, such as multicentric Castleman's disease and primary effusion cell lymphoma (Aaron et al. 2002; Boulanger et al. 2005; Lim et al. 2005; Oksenhendler et al. 1996; Simonelli et al. 2003). Solid tumors may also be increasing, such as bronchogenic carcinoma, melanoma, and renal cell carcinoma, although more data are needed to confirm these initial observations (Bower et al. 2003; Herida et al. 2003).

As opportunistic infections have declined, the causes for hospitalization have changed. The proportion of hospitalizations due to respiratory diseases is still considerable, but has been falling (Grubb et al. 2006). The proportion of hospitalizations due to hepatic disease (especially sequelae of hepatitis C), renal disease (consequences of HIV nephropathy and other disorders), and cardiovascular disease has increased. Among pulmonary complications, the incidence of pneumocystis pneumonia (PCP) has declined, and the fraction of PCP cases that require hospitalization, or admission to the ICU, is falling. Thus, the face of HIV infection in the hospital and in the ICU has changed over the past decade.

We must recognize that there are two distinct populations of patients (Fig. 17.1). First, there are patients with access to care and to the full armamentarium of HIV-related drugs. For these patients, survival is longer and opportunistic complications are fewer, as noted above. These patients are more likely to be admitted to the ICU for non-HIV-related problems, or for complications of their HIV drugs. These patients may eventually lose their responsiveness to antiretroviral therapy (ART), but with opportunistic infection prophylaxis, and perhaps with continuation of ART, they appear to have fewer infectious complications.

Fig. 17.1 The two distinct profile of patients with HIV

Table 17.1 Table summarizing reasons for increased ICU admissions in HIV patients

Reasons for increased ICU admissions in ICU despite HAART era
1. About 25–40% of HIV-infected patients were not known to be positive at the time of ICU admission
2. Around 50% of patients usually were not found to be on effective HAART during admission
3. Number of persons living with HIV has increased as overall survival improved because of effective HAART. So more number of patients living with HIV, is likely to get admitted in ICU
4. Many patients are being admitted to ICU for medical and surgical causes unrelated to their HIV infections such as trauma, post-operative care, asthma, renal failure, liver diseases, and surgical causes

17.3 Etiology and Spread

The HIV epidemic in India is driven by heterosexual sex, which accounted for 87% of new infections. Sex workers, men who have sex with men, people who inject drugs, and transgenders—all four of these groups have been prioritized in the Indian national AIDS response since its inception in 1992.

The epidemiologic profile of patients with HIV infections is shifting. There are a substantial number of homosexual males who are infected in large urban areas, but there is a growing proportion of infected patients who are female, who reside in smaller cities or rural areas, and who have acquired their infection heterosexually or via intravenous drug abuse. The population of HIV-infected patients is also getting older: patients with HIV infection benefit from improved management, and live longer. Individuals without HIV infection are also living longer, and are sexually active longer, extending the period of risk for acquiring HIV infection.

It has been seen that the spectrum of diseases requiring ICU admission is changing in the setting of HAART. Besides, in the HAART era, hospitalization of HIV-infected patients has significantly decreased, but the rate of ICU admissions has not. (Table 17.1).

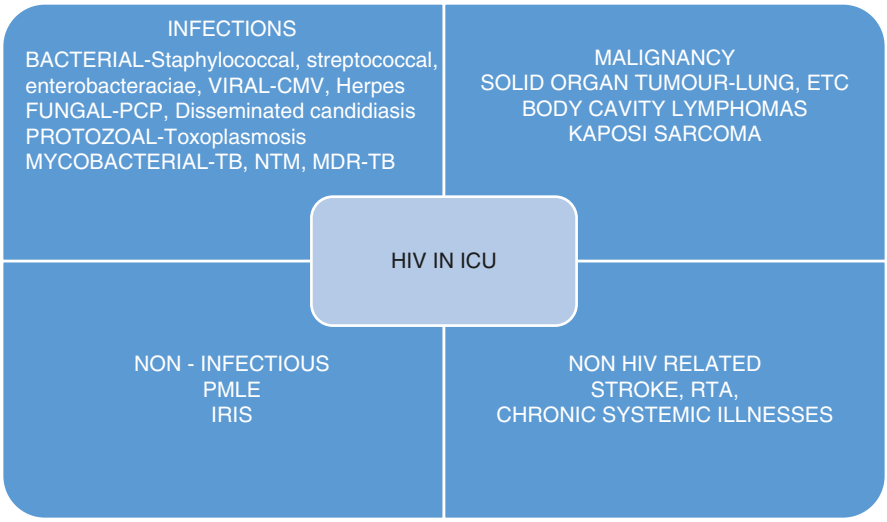

Fig. 17.2 Spectrum of etiologies of ICU admissions of HIV patients

17.4 HIV in ICU: Spectrum

HIV patients may be admitted to ICU for many reasons. Acute respiratory failure as a result of opportunistic infections accounts for approximately half (Sarkar and Rasheed 2013) of ICU admissions which itself can have a myriad of etiologies (Fig. 17.2). Other common indications for ICU admission are sepsis and central nervous system (CNS) dysfunction and complications due to Cryptococcal and Candida meningitis, sub acute encephalitis, herpes simplex encephalitis, multifocal leukoencephalopathy (Casalino et al. 2004; Narasimhan et al. 2004).

Health care professionals should recognize that these patients also become hospitalized for the same reasons that HIV-uninfected patients are admitted (i.e., for HIV-unrelated issues, such as trauma, acute infections, chronic pulmonary disease, chronic coronary artery disease, etc.). These patients need the same management strategies as HIV-uninfected patients with a few exceptions.

There are however, some differences in management (Table 17.2) for HIV-infected patients. First, if they are receiving antiretroviral agents, a decision must be made whether to continue the drugs in the hospital (see below) or whether to discontinue them. Second, certain antiretroviral drugs have profound drug–drug interactions that must be considered when prescribing other agents whose pharmacokinetics might be substantially affected. Third, health care providers need to be cognizant that there is nosocomial exposure to percutaneous or musosal fluids that might be HIV infected; they must take appropriate preventive steps to reduce the likelihood of occupational HIV transmission.

Table 17.2 Table listing the important issues for internists in care of HIV patients in ICU

HIV in ICU—special focus areas
1. Decision to start/continue/stop HAART
2. Drug–drug interactions
3. Opportunistic infections/malignancies
4. Nosocomial spread to doctor/other patients

17.5 Level of Immunosuppression

When a patient with HIV infection presents to a health care provider, it is important to recognize that the patient may or may not have an HIV-related problem. Clinicians often assume that such patients have an opportunistic infection, neoplastic problem, or metabolic disorder that is related to HIV infection, yet such patients are also at risk for common processes. Even if the patient is infected, the infectious process may be caused by a common community-acquired pathogen, and not by an opportunistic pathogen.

CD4 T-lymphocyte counts continue to be excellent indicators of the susceptibility of patients to HIV-related opportunistic infections. The key parameter is the current CD4 T-lymphocyte count, not the nadir count from the past. There are subtle differences in immunologic function based on nadir count that can be dissected by laboratory evaluations, but it is not clear that these differences have major clinical implications (Miller et al. 1999).

17.6 ART in the ICU

When HIV-infected patients are admitted to the ICU, a major issue is whether to continue their ART or stop the drugs. Intensivists need to be aware of several important principles.

1. Antiretroviral agents are only available as oral tablets and suspensions, for the most part. Zidovudine and enfuvirtide are the only agents available in parenteral form. Thus, the pharmacokinetics of ART will be unpredictable in severely ill patients, with uncertain gastrointestinal absorption and potential drug interactions.
2. Protease inhibitors and non-nucleoside reverse transcriptase inhibitors are metabolized by the cytochrome p-450 enzyme system. They alter the metabolism of other drugs metabolized by this system, and they themselves will have their pharmacokinetics altered (Boffito et al. 2005; Flexner and Piscitelli 2003). This may lead to drug toxicity or reduced efficacy.
3. For ART, even a few days of suboptimal levels due to poor absorption or pharmacokinetic interactions can have disastrous results (i.e., irreversible drug resistance can occur).
4. Drug toxicities are often difficult to attribute to a specific drug. Thus, when ART is added to a regimen and potential toxicities such as rash, liver function test abnormalities, or elevated amylase level occur, it is difficult to assess whether it is related to the toxicity of ART or to another drug or disease process. Thus,

discontinuing ART simplifies management of clinical issues that could potentially be due to ART.

5. The initiation of ART for patients in the ICU can cause immune reconstitution syndromes (IRS). These can be life threatening and difficult to distinguish from other clinical syndromes, as described below.

17.6.1 Bacterial Infections

Clinicians should recognize that *Streptococcus pneumoniae* continues to be the most common cause of upper and lower respiratory disease in this patient population. Patients have an increased incidence of bacterial respiratory infections at all CD4 T-cell strata, although the incidence does increase as the CD4 T-cell count declines (Wallace et al. 1997).

A single centered Indian study showed that poly-microbial infection was present in around 20% of the cases (Mane et al. 2018). Studies also show that the incidence of MDR Pneumococcal pneumonia has not changed in pre-HAART and post-HAART era, while there is substantial reduction in MDR Pseudomonas infection. Also MDR Pseudomonas infection correlates with CD4 reduction while higher CD4 counts are related to drug susceptible Pseudomonas infections. Significantly high mortality is seen with MDR Staphylococcal, Pseudomonas, and Klebsiella infections (Allen et al. 2003).

Haemophilus influenzae, both the encapsulated and nonencapsulated types, is also common. There is a growing literature about the occurrence of pneumonia due to *Staphylococcus aureus*, especially oxacillin-resistant strains, and about *Pseudomonas aeruginosa*, especially among patients with low CD4 T-cell counts (Allen et al. 2003; Mathews et al. 2005). The clinical presentation, diagnosis, and therapy for bacterial pneumonia do not differ substantially for HIV-infected patients compared with HIV-uninfected patients. Bacteremia and extrapulmonary disease appear to be more common, at least for *S. pneumoniae*.

17.6.2 Mycobacterial Infections

In most parts of the world, *Mycobacterium tuberculosis* is a major cause of pulmonary and extrapulmonary disease in patients with HIV infection (Kirk et al. 2000; Lawn et al. 2005). Tuberculosis must be a consideration for every patient who presents with pulmonary disease both to facilitate appropriate therapy and to prevent transmission to health care workers, patients, and visitors.

The recognition and management of tuberculosis is a complex process that, unlike the other bacterial diseases above, has many differences in recognition and management in HIV-uninfected patients. Tuberculosis presents in many typical and atypical forms both for pulmonary and extrapulmonary manifestations. The likelihood of disease is estimated to be 10% per year, as opposed to 10% per lifetime for HIV-uninfected individuals.

Treatment of tuberculosis is complicated by the drug interactions of ART agents and antituberculous agents (Gordin 2003; Dean et al. 2002a). Rifampin, in particular, has complex interactions with the protease inhibitors and non-nucleoside reverse transcriptase inhibitors. ART agents and antituberculous drugs also have overlapping toxicities, especially liver adverse events. There are guidelines recommending the appropriate dose and drug adjustments to be made to standard regimens (Panel on Antiretroviral Guidelines for Adults and Adolescents 2019). Treatment of tuberculosis is also complicated by the occurrence of IRIS (Breen et al. 2004; Michailidis et al. 2005; Navas et al. 2002; Shelburne et al. 2002; Shelburne et al. 2005) which is discussed below. Such syndromes associated with recent tuberculosis can be clinically severe and can make initiation of ART a much more complicated endeavor in regions where tuberculosis is common.

M. avium complex clearly causes considerable morbidity in this patient population when patients have CD4 T-cell counts below 50–75 cells/μL. The disease almost always manifests as mycobacteremia, lymphadenitis, or enteritis. Although the lung may be colonized with *M. avium* (i.e., *M. avium* may be readily found in pulmonary secretions), this organism is almost never the cause of pulmonary dysfunction. There are a few documented cases, but in most instances, tissue is needed to be certain that another process is not causing the pulmonary dysfunction. Other mycobacteria occasionally cause pulmonary disease in patients with HIV infection.

17.6.3 *Pneumocystis jiroveci*

Pneumocystis jiroveci (abbreviated PCP to indicate pneumocystis pneumonia) continues to be a common cause of pulmonary disease in developing countries. As indicated above, the outcome of patients with PCP has improved over the past decade. Clinicians are more aware of this entity at CD4 T-cell counts below 200 cells/μL, and diagnosis has improved with the more widespread availability of induced sputum examination and immunofluorescent antibody staining to supplement bronchoalveolar lavage and transbronchial lung biopsy stained with methenamine silver or Giemsa. Clinicians need to be cognizant; however, that about 10–15% of cases of PCP occur at CD4 T-cell counts higher than 200 cells/μL (Chu et al. 1995). Thus, when patients present with pulmonary processes at CD4 T-cell counts greater than 200 cells/μL, PCP should usually not be the first diagnosis considered, but it should not be excluded from the differential diagnosis.

In one study the outcome of HIV negative patients were worse than positive patients. It was proposed that the course of HIV-associated PCP is indolent, leading to better tolerance, unlike in non-HIV patients. But the proportion of patients who fail on NIV was significantly high in HIV-positive patients. Hence a low threshold for intubation is required in patients with HIV. Also the role of corticosteroids is proven when administered in the first 72 h. No evidence is supportive for delayed use of corticosteroids as salvage therapy (Monnet et al. 2008).

PCP usually presents as a subacute illness over several weeks, and the chest radiograph typically demonstrates bilateral, symmetric interstitial infiltrates (Thomas Jr and Limper 2004). However, atypical presentations are not uncommon:

PCP has been documented to produce lobar infiltrates, nodules, cavities, and effusions. Thus, empiric diagnoses on the basis of clinical presentation are less desirable than specific diagnoses on the basis of direct microscopy, culture, or some type of antigen or nucleic acid detection to be certain that the correct pathogen is being treated, and that toxicities of unnecessary drugs are avoided.

Extra pulmonary PCP also occurs in patients with HIV infection. Lesions in the liver and spleen are probably most common. However, lesions in the kidneys, brain, eye, and lymph nodes have also been seen.

The therapy of choice for PCP continues to be trimethoprim–sulfamethoxazole (TMP-SMX); prednisone should be added to patients who present with room air Po2 of less than 70 mm Hg.

For patients who cannot tolerate TMP-SMX or who fail this drug, the most effective alternative is intravenous pentamidine. This drug is well known for its toxicities, which include renal impairment, dysglycemias, and pancreatitis. Dapsone–trimethoprim is effective, but this combination is only available in oral form, and dapsone cross-reacts with sulfamethoxazole in approximately 50% of patients. Thus, this combination offers only modest breadth to the anti-PCP armamentarium. Clindamycin plus primaquine, atovaquone, and trimetrexate are other options. Of these, only trimetrexate can be administered parenterally.

17.6.4 Fungal Pneumonia

Fungal pneumonias (other than PCP) occur in patients with HIV infection, but they are not common in most geographic areas. Cryptococcus, histoplasma, and coccidioides are all recognized to cause focal or diffuse pulmonary disease. In general, diffuse disease is more frequent among patients with CD4 T-lymphocyte counts lower than 200 cells/μL.

Diagnosis and therapy of these pneumonias do not differ substantially from that for disease in other immunosuppressed patients. When these pneumonias occur in patients with low CD4 T-lymphocyte counts, they are difficult to distinguish clinically from PCP. This reinforces the desirability of establishing a specific diagnosis when patients with HIV infection present with pulmonary pathology. For patients with disease and CD4 T-cell counts less than 200 cells/mm^3, therapy must usually be continued throughout life unless immunity is reconstituted by ART.

Aspergillus has been reported as a cause of tracheobronchial or pulmonary disease with increasing frequency (Mylonakis et al. 1998). Patients typically have either a low CD4 T-cell count or neutropenia. The diagnosis may be established by smear- and culture-positive for aspergillus.

The occurrence of candidal infection in HIV patients is high not only in terms of muco-cutaneous infections but also involving invasive infections like candidemia. Studies show that the incidence of candidemia is directly proportional to the level of immunosuppression and extent of muco-cutaneous involvement. Patient who received fluconazole both for treatment and as prophylaxis has high chances of azole resistant candidemia, both albicans and non-albicans. It is also shown that the

removal of central lines along with pharmacological treatment also resulted in complete eradication of the organism when appropriate (Anwar et al. 2012).

17.6.5 Viral Pneumonia

Interestingly, the herpes viruses have not been common cause of pulmonary dysfunction in patients with HIV. CMV is often found in respiratory secretions when patients have low CD4 T-lymphocyte counts, but CMV is rarely the cause of pulmonary dysfunction. Studies have shown, for instance, that the prevalence of CMV in respiratory secretions correlates inversely with the CD4 T-lymphocyte count. It has also been shown that when CMV was present in the lung biopsies of patients with PCP, patients did as well with anti-PCP therapy alone as did patients who had no such inclusions. Thus, to document CMV as the cause of pulmonary dysfunction in this patient population requires tissue demonstrating multiple inclusion bodies and the absence of another likely pathogen.

Herpes simplex virus and varicella-zoster virus have been described as causing pulmonary disease in this patient population. However, this is usually in the setting of disseminated disease when lesions in the skin are apparent. Some cases of herpes simplex virus pneumonia appear to be extensions from the oropharynx, but such cases are unusual in this patient population.

Influenza, respiratory syncytial virus, adenovirus, and coronavirus all cause pulmonary disease in this patient population. However, they are not considered to be HIV-associated opportunistic infections.

17.6.6 IRIS

When ART is initiated in patients with HIV infection, immune function improves as the viral load is reduced and the CD4 T-cell count increases. This improved immunologic responsiveness often manifests as organ dysfunction in response to latent or apparent antigens that can range from mild and clinically unimportant to severe and life threatening. Definition and risk factors are summarized in Table 17.3.

IRIS have been described in case series. Its incidence has been described as varying between 10% and 30% (Dean et al. 2002b; Fishman et al. 2000; Narita et al. 1998; Phillips et al. 2005; Wislez et al. 2001). There are few well-constructed studies defining the immunologic correlates, or the factors that predict their occurrence. From the observational studies published to date, it would appear that the syndrome is most likely to occur in patients who started ART when their CD4 T-cell count is low, typically less than 100 cells/μL, and when their viral load is high, typically greater than 100,000 copies/mL.

The immunopathogenesis of the syndrome is unclear and appears to be result of unbalanced reconstitution of effector and regulatory T cells, leading to exuberant inflammatory response in patients receiving ART. Biomarkers, including interferon-γ

Table 17.3 IRIS-Defintions, Risk factors, Categories and Mechanism

IRIS definition	RISK factors
Samuel generic criteria 1. HIV positive 2. On HAART with decrease in HIV-1 RNA or increase in CD4 count(which may lag) 3. Clinical symptoms consistent with inflammatory process 4. Clinical course not consistent with previous OI/New OI/ Drug toxicity	• ART naïve • Short interval of start of ART • Dramatic fall of HIV RNA • Young age • Lower CD4 count at start of treatment • Genetic susceptibility
French criteria—2 major or 1 major + 2 minor for diagnosis 1. Major- • atypical OI/tumor responding to ART • HIV RNA fall by 1 log 10 copies/mL 2. Minor- • Increase in cd4 • Increase in immune response • Spontaneous resolution	**Categories of IRIS** • Unmasking OI • Paradoxical OI • Auto-immune • Malignancy • Grave disease, etc.
NACO, India Occurrence of new OI in 6 weeks–6 months of starting ART, associated with increase in CD4 count	**Underlying mechanism of IRIS** Mechanism Shift from Th2 to Th1 response

(INF-γ), tumor necrosis factor-α (TNF-α), C-reactive protein (CRP), and interleukin (IL)-2, 6, and 7, are subject of intense investigation at present.

The IRS occurs within weeks or months of starting ART: some syndromes can occur within days, and others, as described below, may not manifest for many months or several years. Because immune function improves qualitatively as soon as the viral load falls, some patients with IRS may not manifest a higher CD4 T-lymphocyte count at the time of the IRS. Alternatively, some patients with organisms in a sequestered focus, such as bone, are more likely to have the late manifestations.

These IRS appear to be most common in areas where tuberculosis or cryptococcosis is common. The relationship of IRS to specific pathogens is being defined. Some experts report, for instance, that IRS rarely occurs due to latent *M. tuberculosis*, but commonly occurs due to latent *M. avium* complex. IRS commonly occurs after active tuberculosis is diagnosed. For CMV retinitis, IRS can occur weeks, months, or years after the CMV retinitis is stabilized by drug therapy if ART is belatedly initiated.

There is no consensus case definition of IRS, and thus the literature includes reports that categorize clinical manifestations differently. It is extremely difficult when a patient presents with a new clinical syndrome after starting IRS to determine if the manifestation is an immunologic reaction that needs no specific intervention, or whether the process represents an active opportunistic infection in need of therapy. Some series include patients with fungemia or mycobacteremia as examples of IRS. Other series would include such patients as cases of active or new opportunistic infections in need of specific therapy. These uncertainties leave the clinician with a dilemma about how aggressive to be diagnostically or therapeutically.

Some syndromes have been managed without therapy. Some syndromes that were clinically more severe have been treated with antiinflammatory agents, including prednisone. Other syndromes have been treated with long courses of specific antiinfective therapy.

Studies show that it is prudent to start ART after 2 weeks of initiation of ATT but no later than 8 weeks. But no much clarity exists for other opportunistic infections. In general, it appears prudent that ART should be initiated before the onset of severe immunodeficiency and after the treatment of opportunistic infection. But the benefit of delaying ART initiation should not unnecessarily curb the treatment of HIV in case of severe disease. Regardless of presence of absence of infection, it is advisable to start ART with CD4 count less than 50 (Sharma and Soneja 2011).

All the above mentioned infections and IRIS can present with repiratory failure requiring ICU admission. Besides altered senosium due to CNS—tuberculosis, cryptococcosis, toxoplamosis, PMLE, HIV encephalopathy, etc. can also be a cause for intensive care.

Mild IRIS can be treated with NSAIDS. Life threatening or those with organ dysfunction need steroid use. It should be clear that using steroid in presence of inappropriate dosage of treatment of OI may inadvertently worsen the same. Hence treatment optimization for OI is needed, taking into consideration of all possible drug interactions (Sharma and Soneja 2011).

17.7 Neoplastic Disease

Kaposi's sarcoma and lymphoma are well-recognized causes of pulmonary disease in patients with HIV infection. The incidence of Kaposi's sarcoma has declined as the epidemic has moved into heterosexual individuals and women, groups that do not characteristically have a high incidence of Kaposi's sarcoma. In addition, ART use has been associated with a decline in this tumor, which is linked to HHV-8 infection.

When Kaposi's sarcoma does occur in the lung, it presents as patchy bronchial lesions (Aboulafia 2000; Cadranel et al. 1994; Hartman et al. 1994; Huang et al. 1996; Tirelli et al. 2000). Often, there is an associated pleural effusion that is bloody when thoracentesis is performed.

The diagnosis is often anticipated by concurrent skin lesions and the presence of prominent lesions in the tracheobronchial tree, which are easily recognized by bronchoscopy. The diagnosis is not easy to establish definitively.

Transbronchial biopsies of the bronchus or lung parenchyma reveal crush artifact that is hard to distinguish from Kaposi's sarcoma. On cytology, there is no diagnostic feature. Thus, either tissue must be obtained on open lung biopsy or video-assisted thoracoscopy, or a presumptive diagnosis must be made when Kaposi's sarcoma in seen in the tracheobronchial tree and bronchoalveolar lavage reveals no other likely pathogens.

Pulmonary Kaposi's sarcoma can respond well to chemotherapy (Dupin et al. 1999; Holkova et al. 2001; Lichterfeld et al. 2005; Martin-Carbonero et al. 2004).

The use of ART and opportunistic infection prophylaxis has contributed to the success rates of management strategies.

Lymphoma continues to be a cause of pulmonary disease (Bazot et al. 1999; Eisner et al. 1996). Although primary CNS lymphomas have greatly diminished in frequency in patients treated with ART, primary B-cell lymphomas elsewhere continue to occur. Patchy pulmonary infiltrates have been well described. Biopsy or cytology is needed to establish a diagnosis.

Combination chemotherapy for HIV-associated lymphoma has become impressively more successful when ART is continued with opportunistic infection prophylaxis (Little et al. 2003; Ratner et al. 2001; Re et al. 2003). Some regimens provide a brief drug holiday while the patients is actively receiving chemotherapy to avoid problems with drug absorption or drug interactions. However, it would appear that active ART and opportunistic infection prophylaxis are important elements contributing to improved survival. Stem cell transplantation has also been used successfully (Krishnan et al. 2005; Serrano et al. 2005).

As life expectancy in HIV is increasing and the literature is evolving, other pulmonary neoplastic processes have been recognized that clinicians should be aware of. Primary effusion cell lymphoma can present in the pleural, pericardial, or abdominal cavities, and presents as effusions. Primary effusion lymphomas are always associated with human herpes virus 8 (HHV8), and sometimes with Ebstein barr virus (EBV) also. They are often diagnosed by cytopathology and resistant to conventional chemotherapy. Treatment guidelines invariably include continuing HAART with chemotherapy and prognosis remains poor. It is not clear how effective chemotherapy is for this tumor.

A multi-centric European study showed that the degree of disease progression is directly proportional to the nadir CD4 values more than the proximal CD4 values. The presence of opportunistic infection, for which the patient is admitted, will influence the level of CD4 count; hence CD4 count of the current admission may not be reliable. It was also noted that the viral load was significantly higher in patients who were not receiving ART, but with high CD4 count than those with relatively low CD4 count, in spite of being on ART. Arguments were raised that those patients with high CD4 count would not have taken ART as they would have been asymptomatic, and hence their viral load tends to be higher. But this does not hold good in today's scenario, since all diagnosed HIV-positive patient should be started on ART. It should also be remembered that the level of immunosuppression is interplay of CD4 counts, both proximal and nadir, viral load, duration, and compliance with ART, level of disease progression before the current admission. No single parameter should be used to conclude the level of immunosuppression (Miller et al. 1999).

Multicentric Castleman's disease is another unusual neoplastic process that is associated with HIV infection (Hillier et al. 2004). This HHV-8 process can present with pulmonary infiltrates, as well as fever, lethargy, adenopathy, and cytopenias. Diagnosis usually requires a combination of HHV-8 titers and bone marrow or lymph node tissue, plus flow cytometry (Oksenhendler et al. 2000). Patients often develop lymphoma and/or Kaposi's sarcoma subsequently. It is unclear how effective any therapy is for this disease.

Several large databases have suggested that certain solid tumors can be overrepresented in this patient population (Braun et al. 1990; Tenholder and Jackson 1993). Bronchogenic carcinoma as well as melanoma, colon cancer, and breast cancer appear to occur with increased frequency even when other risk factors are considered.

17.8 Drug Toxicities

Several antiretroviral agents have toxicities that can present with pulmonary or respiratory manifestations.

When patients receive ART regimens that contain abacavir, they can develop a hypersensitivity syndrome that is difficult to distinguish from nonspecific febrile respiratory illnesses (Tenholder and Jackson 1993; Escaut et al. 1999; Hewitt 2002; Keiser et al. 2003; Walensky et al. 1999). However, because abacavir hypersensitivity reactions can be fatal, this syndrome must be recognized. Patients present during the initial 4–8 weeks of abacavir therapy with fever, rash, fatigue, nausea, or vomiting. About 20% of patients will have cough; some of these patients have been described to have pulmonary infiltrates.

The syndrome usually persists unless the drug is discontinued. A feature that clinicians must be aware of is the danger of "rechallenge." Patients with this syndrome may stop taking their drugs due to their systemic illness, or their nausea and vomiting. Cases of distributive shock, some fatal, have occurred on rechallenge. Thus, most experts would recommend that if a potential syndrome occurs, and the drug is discontinued, rechallenge should not be permitted. There is a link between abacavir hypersensitivity syndrome and HLA B27, but it is not clear yet whether screening patients for this genotype would be cost-effective.

Another drug toxicity that can present with dyspnea occurs when patients have been receiving nucleoside antiretroviral agents for long periods of time (Gerard et al. 2000). Any of the nucleosides (zidovudine, stavudine, didanosine, lamivudine, abacavir, emtricitabine) can probably cause this syndrome, although it is best described with didanosine and stavudine. This syndrome is a reflection of mitochondrial toxicity. Patients with this syndrome are often female and obese. Hepatic steatosis is frequently associated with the disease. Patients present with weakness and fatigue, and eventually develop lactic acidosis. Serum lactate levels are typically considerably above 5 mmol/L. These patients may appear to be septic, although they are not usually febrile. The only effective therapy is to stop the drug: other interventions, such as carnitine or riboflavin, have no documented benefit. Whether patients can subsequently be safely rechallenged with other nucleosides has not been well studied, although abacavir, lamivudine, and FTC seem to impart very little risk.

17.9 Precautions: The Key to Prevention

The use of universal precautions in the ICU cannot be over-emphasized for the safety of everyone—hospital staff, other patients, and the HIV patients' relatives. These should be pasted in ICU to ensure strict compliance

1. Personal protective equipment.
   (a) Wear gloves when handling infectious material or where there is a possibility of exposure to blood or other body fluids.
   (b) Discard gloves whenever they are thought to have become contaminated wash your hands and put on new gloves.
   (c) Do not touch your eyes, nose, or other exposed membranes or skin with gloved hands.
   (d) Do not leave the workplace or walk around the laboratory wearing gloves.
   (e) Wash your hands with soap and water immediately after any contamination and after work is completed. If gloves are worn, wash your hands with soap and water after removing gloves.
   (f) Wear a laboratory gown, overall, or uniform when in the laboratory. Wrap-around gowns are preferable. Remove this protective clothing before leaving the laboratory. Eye-covers and masks should also be worn.
   (g) Keep the ICU clean, neat, and free from extraneous material and equipment.
2. Disinfection
   (a) Disinfect work surfaces when procedures are completed and at the end of each working day. An effective all-purpose disinfectant is a hypochlorite solution with a concentration of 0.1% available chlorine (1 g/L, 1000 ppm).
   (b) Spills of infected or potentially infected material should first be covered with paper towelling or other absorbent material. A disinfectant should be poured around the spill area and then over the absorbent material and left for 10 min. The standard disinfectant recommended for cleaning contaminated surfaces is a hypochlorite solution with a concentration of 0.5% available chlorine (5 g/L, 5000 ppm). However, for laboratories working with HIV cultures and virus preparations, a higher concentration of available chlorine (1.0%) is recommended.
   (c) Needle-stick or other puncture wounds, cuts, and skin contaminated spills or splashes of specimen material should be thoroughly washed with soap and water. Bleeding from any wound should be encouraged.
   (d) All spills, accidents, and overt or potential exposure to infectious material should be reported immediately to the laboratory supervisor. A written record should be kept of all such incidents. Appropriate medical evaluation, surveillance, treatment and, if necessary, counselling should be provided.
   (e) Handwashing using all steps should be strictly followed before and after any exposure/procedure/patient handling.
3. Sharps handling
   (a) Whenever possible, avoid using needles and other sharp instruments. Place used needles, syringes, and other sharp instruments and objects in a puncture-resistant container. Do not recap used needles and do not remove needles from syringes.

17.10 Conclusions

The clinical features of patients with HIV infection who present to ICUs have changed over the past 25 years. As patients with HIV infection live longer, more are being seen in ICUs for issues unrelated to their HIV infection. When they are admitted to the ICU, for whatever reasons, intensivists need to be knowledgeable about the complex issues related to efficacy and toxicities of ART. New manifestations, such as IRS and premature atherosclerosis, are emerging. HIV-infected patients in the ICU are clearly a population that requires special expertise for optimal management.

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Clostridium Difficile Infection—Diagnosis, Treatment and Prevention

18

Anil Kumar and Debyani Dey

C. difficile is a leading cause of hospital associated gastrointestinal illness, placing high economic burden on the healthcare system. Once thought to be a commensal, it has now emerged as a major enteric pathogen with worldwide distribution. Patients with CDI typically have extended lengths of stay in the hospital and it frequently causes large hospital outbreaks (Cohen et al. 2010).

C. difficile is a gram positive, spore forming bacteria, with feco-oral transmission. It colonises the large intestine and releases two protein enterotoxins (TcdA and TcdB) that causes colitis in susceptible patients. Diarrhoea is mediated by the toxins which inactivate members of the Rho family of guanosine triphosphatases, leading to colonocyte death, loss of intestinal barrier function and neutrophilic colitis. The disease spectrum varies from asymptomatic carriage, to mild diarrhoea, to colitis, or pseudomembranous colitis. Factors determining clinical expression of disease are virulence of infecting strain and the host immune response (Daniel 2015).

A hypervirulant strain of C. difficile, the North-American pulse field gel electrophoresis type 1 (NAP1) strain, has been attributed to cause a severe form of disease. Patient with this strain undergoes more urgent colectomies and have an overall mortality of 17%. The severity is believed to be due to an overproduction of toxin A and B by about 15–20 fold, caused by a deletion in the regulatory gene, TcdC. Outbreaks of the NAP1 strain are supposed to be caused by fluoroquinolones primarily, though others have also been implicated (O'Connor et al. 2009; Pepin et al. 2007).

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18.1 Case Definitions (Cohen et al. 2010)

CDI has a wide range of clinical manifestations from mild self-limiting diarrheal illness to a fulminant life threatening colitis. Onset of symptoms range from1 day to up to 10 weeks after antibiotic administration. Most cases occur between 3 and 7 days of exposure. The watery diarrhoea is accompanied by fever and mild abdominal cramps.

CDI is defined as the acute onset of diarrhoea with documented toxigenic *C. difficile* or its toxin and no other evident cause for diarrhoea (Cohen et al. 2010).

Type of case	Definition
Healthcare facility onset healthcare facility associated (HO-HFCA)	Occurs when onset of symptoms 3 days after admission to a healthcare facility
Community onset healthcare facility (CO-HCFA)	Onset of symptoms within 4 weeks after being discharged from a healthcare facility
Community associated (CA)	Occurs when the onset of symptoms occurs outside a healthcare facility or during first 48 hrs of admission and no prior admission to healthcare facility in the last 12 weeks
Indeterminate or unknown onset	CDI occurs after being discharged from a healthcare facility 4–12 weeks previously
Recurrent CDI	Episode of CDI that occurs 8 weeks after the onset of a previous episode provided the symptoms from earlier episode resolved

Rates of CDI have been increasing since 2000, particularly in elderly with recent hospitalisation or residing in long-term care facility (LTCF). Carriage of C. difficile occurs in 5–15% healthy adults, may be as high as 84% in newborns and infants, and up to 57% in residents in Long-Term Care Facility. Transmission in healthcare facilities is as a result of surface and environmental contamination and hand carriage by staff members and infected patients.

18.2 Risk Factors

Exposure to antibiotics (Cephalosporin, Clindamycin, Fluoroquinolone)

Exposure to organism

Comorbid conditions including Inflammatory Bowel Disease

GI tract surgery

Medications that reduce gastric acid (including PPI)

The usual acidic environment of the stomach is fatal to the spore of *C. difficile* and thus makes germination in the colon less likely. PPIs also cause an alteration in the gastrointestinal flora that allows *C. difficile* colonisation (Janarthan et al. 2012).

Nasogastric tube feeding- increases the risk of infection by contamination of feeding formula or equipment during handling and by an alteration of the colonic

environment associated with special formulae. Risk is greatest when patients are fed with a post-pyloric tube (O'Keefe 2010).

Organ transplantation, chemotherapy
Chronic kidney disease
Immunodeficiency.

18.2.1 Guidelines for Diagnosis of CDI (Christina et al. 2013)

CDI is diagnosed by presence of toxigenic strain of C. difficile or one of its toxins in the stool. Isolating the organism is expensive, time consuming and usually insufficient due to the presence of non-toxigenic C. difficile in the stool.

Following are the diagnostic tests for *C. difficile*

C. difficile culture—false positive rate of around 10% if used alone. Further analysis is needed to determine presence of toxin A, B or the virulence factor genes.

Toxigenic culture.

CCNA C. difficile cytotoxin neutralisation assay—when filtered diarrheal stool is added to cultures fibroblasts a characteristic pathologic effect is seen. If toxin is present in the filtrate, it causes the fibroblasts to round up in a characteristic cytopathic effect. The cell assay is now largely replaced by ELISA.

ELISA can detect both toxin A and B, sensitivity is near 90% in comparison to cytotoxicity assay.

EIA [enzyme immunoassay] for GDH glutamate dehydrogenase—glutamate dehydrogenase is an enzyme produce by C. difficile in relatively large amounts compared with toxins A and B. It is not very specific and there is some cross reaction with the same enzyme in other non-toxigenic clostridial species.

Toxin EIA tests [enzyme immunoassay]—widely used earlier, but have reduced sensitivities compared with reference standards.

NAATs nucleic acid amplification tests such as PCR—good stand-alone tests.

1. Only stools for patients with diarrhoea should be tested for *C. difficile*. In cases of patient with complicated disease and ileus, rectal swabs can be used for timely diagnosis.
2. Nucleic acid amplification tests (NAAT) for *C. difficile* toxin genes such as PCR are superior to toxins A + B EIA testing as standard diagnostic test for CDI.
3. Glutamate dehydrogenase (GDH) screening tests for *C. difficile can* be used in two or three step screening algorithms with subsequent toxin A and B EIA testing, but the sensitivity is lower than NAAT.
4. Repeat testing should be discouraged and testing for cure should not be done.

Endoscopy p may be a useful adjunct in some cases if diagnosis is not confirmed by stool testing or compatible clinical syndrome. The findings are colonic oedema, erythema and mucosal ulcerations, or the pathognomoic pseudomembrane. Most lesions are visible within 60 cm from the anus so either flexible sigmoidoscopy or colonoscopy can be done.

CT is rarely used in the diagnosis except for complicated cases. Findings are colonic wall thickening>4 mm, wall nodularity, pericolonic stranding and ascitis. Less common findings include distension of the colon, colonic fold effacement and nodular fold thickening. CT image findings do not correlate very well with disease severity (Kirkpatrick and Greenberg 2001).

18.2.2 Management of Mild Moderate and Severe CDI (Christina et al. 2013)

Treatment of CDI is done on the basis of severity of disease. It may progress even after treatment has been initiated so assessment must be a dynamic process.

First step is cessation of inciting antibiotics. If unsafe to stop, it is advisable to change over to a narrow spectrum drug.

Metronidazole and vancomycin are the most commonly used antibiotics used to treat CDI. Both are administered orally in patients able to tolerate the oral route. Metronidazole may also be given intravenously as biliary excretion and exudation across the inflamed mucosa allow therapeutic concentrations in the colon. IV vancomycin is not effective as the drug concentration is low due to minimal bowel excretion.

Metronidazole is the appropriate first line drug for mild to moderate disease. In a RCT that compared metronidazole to vancomycin for severe CDI in 150 patients, cure rate with metronidazole was only 76% compared to 97% with vancomycin. Due to this, vancomycin is the drug of choice for severe CDI or with risk factors for progressing to severe disease.

In severe CDI with absent or reduced bowel motility, intracolonic administration of vancomycin has a better treatment result. If the colitis is extreme and the efficacy of antibiotic therapy is doubtful, surgical consultation for colectomy should be obtained. Elderly patients with leucocytosis and elevated lactate appear to benefit most from surgery during NAP1 epidemics. Admission to the hospital for a diagnosis other than CDI, mental status changes, vasopressor support are all predictors of post-operative mortality.

Other antibiotics such as rifampicin, nitazoxanide and fusidic acid have equal or poorer results in the treatment of CDI. A novel macrocycle antibiotic OPT-80 is being evaluated for the treatment of CDI. It is minimally absorbed from the gut and well tolerated. It is highly effective against C. difficile but leaves majority of the GIT gram-negative bacteria intact.

Neutralising the toxin has also been tried as a treatment strategy, cholestyramine and colestipol were evaluated for binding the toxin, but in vivo results are not satisfactory.

Mild disease—CDI with diarrhoea as the only symptom

Moderate disease—CDI with diarrhoea but without additional symptoms/signs meeting the definitions of severe or complicate CDI.

18.2.3 Treatment of Mild to Moderate Disease

If pretest probability of CDI is very high empiric treatment of CDI should be considered regardless of laboratory results as negative predictive values of lab tests are not high enough to exclude the diagnosis.

Metronidazole 500 mg orally TDS for 10 days. If unable to take MN, vancomycin 125 mg orally four times a day for 10 days

Severe disease CDI that presents with or develops during the course of illness with—hypoalbuminemia (<3 mg/dL) and either of the following

WBC > =15,000 cells/mm^3 or

abdominal tenderness without criteria of complicated disease

18.2.4 Treatment

Vancomycin as above 125 mg QID for 10 days

18.2.5 Complicated Disease

CDI that presents with or develops at least one of the following signs or symptoms:

- ICU admission
- Hypotension with or without inotropes
- Fever >38.5 Celsius
- Ileus or significant abdominal distension
- Mental status changes
- WBC > = 35,000 or < 2000/mm^3
- serum lactate >2.2 mmol/L
- Evidence of end organ failure.

Vancomycin orally 500 mg four times a day and Metronidazole 500 mg IV every 8H vancomycin 500 mg in 500 ml saline as enema rectally four times a day. Surgical consultation suggested.

18.2.5.1 Recurrent CDI

Treatment with long course of oral vancomycin either in a tapering or pulse dosing schedule is appropriate for patients with recurrent disease. Recent studies have attempted to use a 2 week therapy with rifamixin after a standard course of vancomycin.

Recurrent disease—within 8 weeks of completion of therapy.

18.2.5.2 Treatment

Repeat metronidazole or vancomycin pulse regimen. Consider FMT fecal microbiota transplantation after three recurrences.

18.3 Prevention of CDI

In the present era, hospital infection control practises focussing on the prevention of CDI has been the focus of a lot of interest, particularly in the application of bundle care for prevention. That bundle care helps in decreasing incidence of CDI has been well established (Muto et al. 2007).

These are divided into five major care bundles:

- Antimicrobial and drug management bundle.
- Detection bundle
- Practise bundle
- Cleaning bundle
- People bundle—focussed on training and implementing care bundles by teaching staff and families about CDI prevention.

18.3.1 Antibiotic and Drug Management Bundle

Evidence based management and treatment of CDI.
Judicious use of antibiotics.
Robust antibiotic stewardship programme.
Assess use of proton pump inhibitors.
Educating providers and patients.

18.3.2 Detection Bundle

Early recognition and simple diagnostic testing criteria.
Proper collection and handling of specimens (timeframe and temperature).
Appropriate testing—PCR, Antigen toxin assay
Retesting criteria—no testing for cure.

18.3.3 Practise Bundle

Early isolation, cohorting of patients if isolation not feasible.
Contact precautions—gowns, gloves, signage, meticulous hand hygiene.
Dedicated disposable equipment should be used, proper disinfection if reusable.

18.3.4 Cleaning Bundle

Identify C. difficile infected environmental surfaces and equipment for cleaning.
Use of checklists for daily and terminal cleaning.
Appropriate dwell time for cleaning solutions.

Competency assessment of housekeeping staff for compliance to cleaning instructions.

18.3.5 People Bundle

Administrative support for the CDI prevention programme.

Involve and educate patients and families.

Educate all staff about CDI, transmission and prevention.

Collaborative efforts beyond the hospital to change prescription practises and increase awareness.

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Infections in the Intensive Care Setting: Role of Radiology

19

Naren Hemachandran and Devasenathipathy Kandasamy

Imaging plays a vital role in the diagnosis and management of a wide range of infections and their associated complications in the intensive care unit (ICU). A wide range of modalities is available nowadays, even at the bedside, increasing the armamentarium of resources available to us. The understanding of the modalities with specific knowledge of the advantages and disadvantages of each of these modalities would enable optimal utilization of resources, prompt management of various conditions with better clinical outcomes.

A radiograph is often the first investigation done in a patient suspected of having an infection on clinical grounds in the ICU setup, especially in suspected chest infections. This is not only due to the limited utility of the physical examination in the intensive care setup but also due to the widespread availability of bedside radiography machines. However, radiographs may not always be diagnostic due to the low sensitivity and specificity of the findings. Usage of sub-optimal radiographic technique in the ICU setting, and the presence of monitoring and other devices (either in or on the patient) that obscure parts of the exposed field as well hinder in the interpretation of the pathological findings (Bekemeyer et al. 1985; Henschke et al. 1983; Janower et al. 1984).

Ultrasonography (USG) is increasingly used in the ICU setup due to its immediate bedside availability and the ease of performing it without the need for technicians (as for radiographs/CT). It is a useful adjunct to radiographs and helps in diagnosing and differentiating certain non-specific findings on the radiograph. Also, USG can be used for performing image-guided procedures like draining fluid/collections or for diagnostic aspiration.

Computed Tomography (CT) is predominantly used as a problem-solving tool in the ICU setup as usually the patient needs to be shifted to the CT suite for the scan. Hence acutely ill or unstable patients need to be stabilized initially before a CT can be performed. Also, there is nearly 100 times greater radiation exposure with a CT

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compared to a routine chest radiograph (Mettler et al. 2008). CT plays an important role in the CNS due to the limited utility of radiographs and USG.

Magnetic Resonance Imaging (MRI) is rarely used in the ICU mainly due to its long acquisition times and the resultant need for sedation/anesthesia. Initially, MRI was predominantly used for CNS imaging due to a lack of motion-related artifacts. However, with technological advances and the availability of faster sequences, it is increasingly used as a problem-solving tool in the chest and abdomen as well.

The utility of imaging modalities in various clinical situations is discussed as per various organ systems involved.

19.1 Chest

Chest radiographs were widely obtained on a daily basis in the ICU setup previously (Figs. 19.1 and 19.2). However, studies have shown that routine daily chest

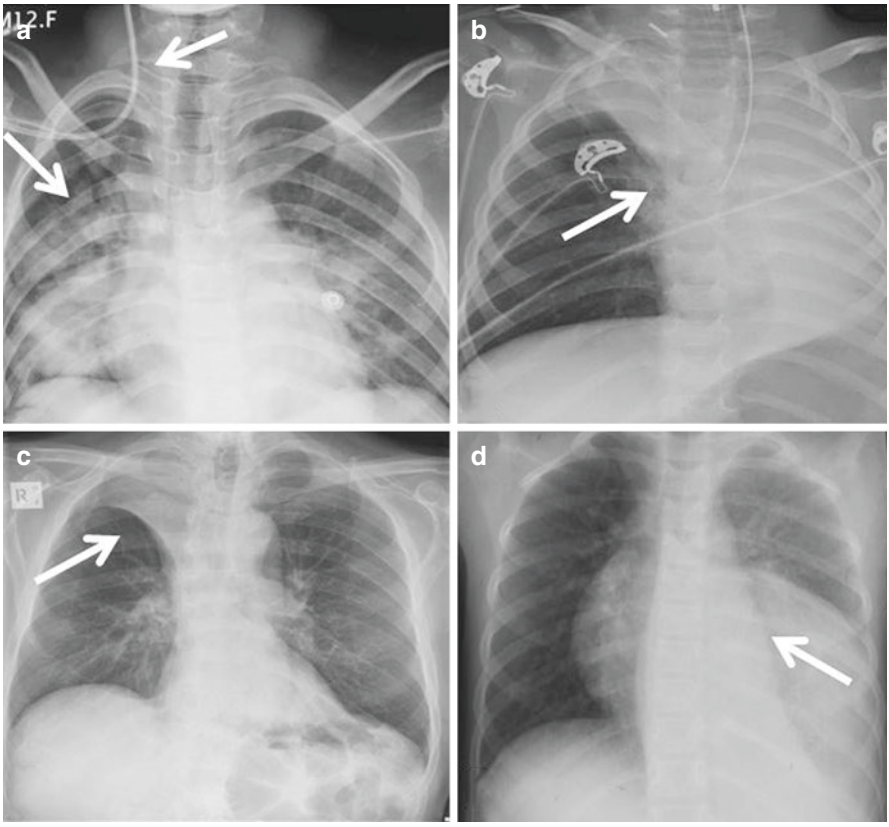

Fig. 19.1 Different patterns on Chest Radiograph—(**a**) Typical fluffy air space opacities with air bronchogram in a bilateral perihilar location in a case of pulmonary edema. There is also an incidental mal-positioned central venous catheter. (**b**–**d**) Collapse—mal-positioned ET position into the right bronchus intermedius causing a collapse of the entire left lung and the right upper lobe (**b**), collapse of right upper lobe (**c**), typical triangular retrocardiac opacity obscuring the left hemidiaphragm in a case of left lower lobe collapse (**d**)

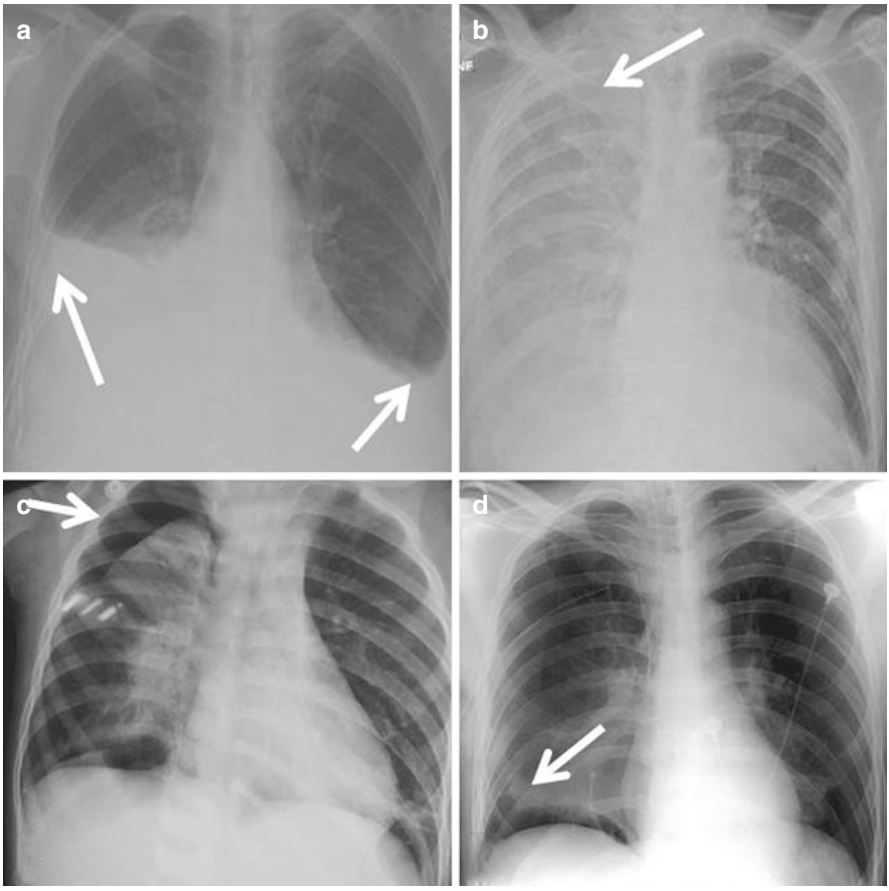

Fig. 19.2 Pleural pathologies on chest radiograph—Bilateral effusion with blunting of the cardiophrenic angles and meniscus formation (**a**). Homogenous veil like opacity in the right hemithorax in a supine radiograph in a patient with right side effusion (**b**). Pneumothorax with the collapsed right lung (**c**). Supine radiograph showing right pneumothorax with prominent deep sulcus sign (**d**)

radiograph is not indicated for all patients in the intensive care setup. The American College of Radiology (ACR) considered daily portable CXRs most appropriate for patients receiving mechanical ventilation (MV) until 2008. However, later work revealed that patient-centered outcomes (e.g., mortality, length of stay, and duration of MV) are not associated with routine daily CXRs. Based on this, the ACR recommendations were amended. In 2014, the entire category of patients receiving MV was removed and routine CXRs in all stable patients in the ICU were categorized as "usually not appropriate." In patients with a central venous catheter, a Swan-Ganz catheter, a feeding tube, or a chest tube placement, only postprocedure radiographs are indicated. Stable patients with cardiac diseases and those with purely extrathoracic disease require only admission films upon entry into the ICU (Amorosa et al. 2013; Soo and Edey 2012; Savoca et al. 1978; Godoy et al. 2012a; Godoy et al. 2012b).

Chest USG enables prompt differentiation of pleural effusion vs. consolidation and also helps in bedside image-guided interventions enabling better precision, improved outcomes with lesser chances of failed attempts (Fig. 19.3).

Some of the common infective pathologies of the chest encountered in the intensive care setting are discussed below.

Aspiration It is common in ICU patients. It can be divided into three forms: Aspiration pneumonitis, aspiration pneumonia, and central airway obstruction. The severity of aspiration would depend on the type and volume of the aspirate. Risk factors include general anesthesia, depressed consciousness, neuromuscular disorders, esophageal disease. Focal or multifocal consolidation in the dependent parts of the lungs is the most common radiographic finding. Acinar filling results in poorly defined nodules in an airway distribution. Other findings include airway wall thickening and plugging, and associated volume loss. Aspiration pneumonitis usually shows clearing within the first few days. A lack of clearing or progression is sugges-

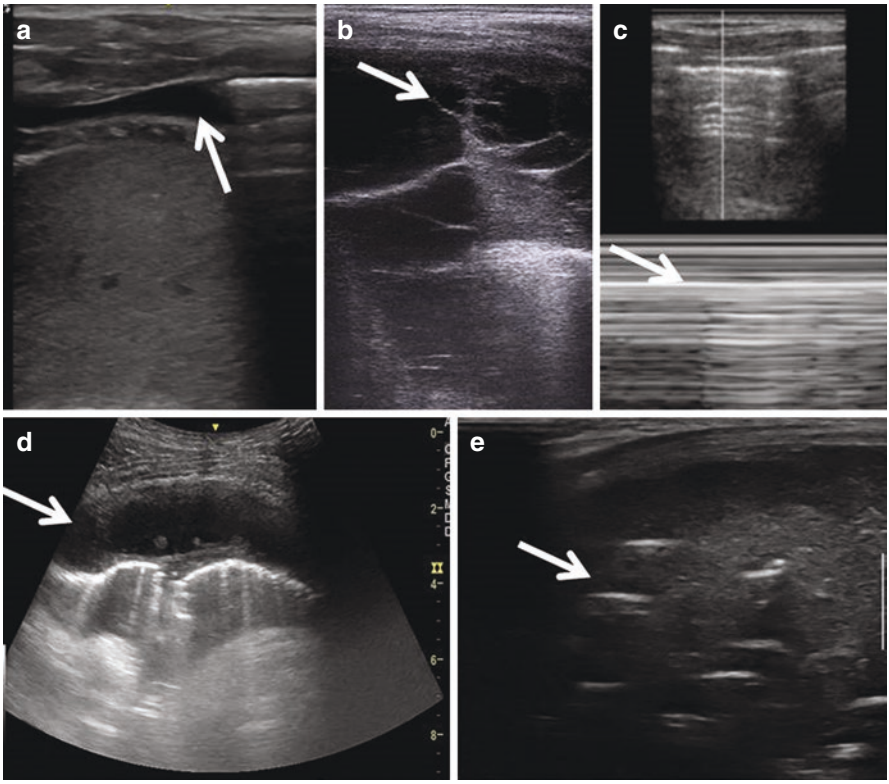

Fig. 19.3 Chest ultrasonography: The high sensitivity in the detection of minimal effusion demonstrated as a thin anechoic streak (**a**). Moderate effusion with septae debris (**b**), associated pleural thickening and collapsed lung (**c**). Homogenous echogenicity with linear streak artifacts (air bronchogram) in consolidation (**d**). Stratosphere sign on M-mode in a case of pneumothorax (**e**)

tive of the development of pneumonia. In the supine position (typical of ICU setup), the aspiration is typically located in the posterior aspect of the upper lobes, the superior and posterior basal segments of the lower lobes resulting in a central predominance on the AP supine radiograph (Lee and Ryu 2018; Hu et al. 2015; Newman et al. 1982; Shifrin and Choplin 1996; Prather et al. 2014; Franquet et al. 2000).

Pneumonia In the ICU setup, it is usually Hospital-acquired pneumonia (HAP—lower respiratory infection manifesting clinically 2 or more days after hospital admission) or Ventilator acquired pneumonia (VAP—lower respiratory infection manifesting clinically 2 or more days after intubation). Gram-negative bacteria are the most frequently implicated in HAP. Radiographic changes in pneumonia typically occur more slowly than in atelectasis, aspiration, or pulmonary edema. It is generally impossible to specifically identify the causative organism based on the radiological appearance; however, there are some general radiological patterns that enable us to narrow down on the list of differential diagnosis (Tarver et al. 2005; Katz and Leung 1999; Reynolds and Banerjee 2012; Langer and Haeusler 2009).

Various radiological patterns and the commonly associated organisms include

- Lobar consolidation—Streptococcus pneumoniae, Klebsiella pneumoniae, Pseudomonas aeruginosa
- Necrotizing pneumonia/cavitation/lung abscess—Staphylococcus aureus, gram-negative bacteria including Acinetobacter baumannii, rarely Candida albicans
- Bronchopneumonia—Staphylococcus aureus, gram-negative bacteria, aspergillosis, atypical organism like Mycoplasma (peribronchial nodules and bronchial wall thickening)
- Interstitial—infrequent pattern—viral infections
- Nodular—Septic emboli (Staphylococcus aureus), Angioinvasive fungal infections (immunocompromised host)

Complications Radiology plays an important role in the early diagnosis of various complications and prompt image-guided interventions would prevent further clinical deterioration. Various complications include (Fig. 19.4)

- Pulmonary—Lung abscess, gangrene, ARDS.
- Pleural—Synpneumonic effusions and empyema due to *Staphylococcus aureus*, gram-negative bacteria; Pneumothorax in cavitatory infections especially in ventilated patients; bronchopleural fistula.
- Vascular—Pulmonary hemorrhage, vascular thrombosis, pseudoaneurysms.
- Others—Chest wall osteomyelitis, empyema necessitans, etc.

ARDS, pulmonary embolism, pulmonary edema, and atelectasis can mimic pneumonia especially in the ICU setting and a multidisciplinary approach with a clinical-radio-pathological discussion would be needed to differentiate these from

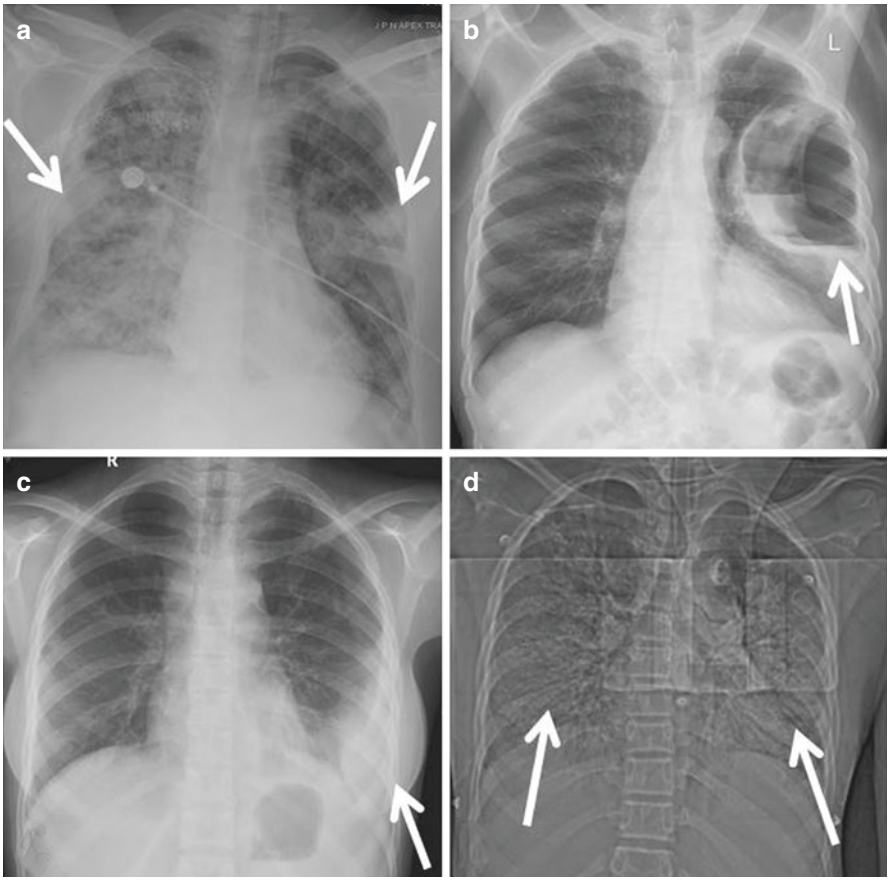

Fig. 19.4 Pneumonia and its complications—Patchy air space opacities in bilateral lung fields in a case of bronchopneumonia (**a**), lung abscess with air-fluid level (**b**), empyema with loculated collection (**c**), patchy bilateral air space opacities in ARDS (**d**)

pneumonia and its above-described complications (Vilar et al. 2004; Lampichler 2017; Klein et al. 1995; Light et al. 1980; Mueller and Berlin 2002).

19.2 Central Nervous System

Neurological infections constitute an important etiological cause requiring admission to ICU. In addition, health-care associated neurological infections, including those that develop as complications secondary to various procedures, may develop in critically ill patients admitted to an ICU for other indications. Although bacterial infections are the most common cause, mycobacterial and fungal infections are also frequently encountered. The single most important prognostic factor is the delay in institution of specific treatment and thus timely diagnosis is of utmost importance.

Patients with CNS infections usually present with altered sensorium which may or may not be accompanied by fever. Both CT and MRI are useful in the evaluation of CNS infections; however, MRI is more sensitive than CT in the evaluation of both meningeal and parenchymal inflammation. MRI with or without IV contrast is the most appropriate imaging according to the ACR appropriateness criteria in a suspected case of meningitis/encephalitis (Douglas et al. 2014). However, this is usually not possible in the ICU setting and hence CT scan is the initial investigation most of the time.

The use of IV contrast not only enables the radiologist to identify abnormal meningeal enhancement (although low sensitivity) that can be seen in meningitis but also increases the sensitivity for identification of intra-axial complications like a cerebral abscess, etc. which are discussed in further detail in later sections. Prior to administration of iodinated contrast, most radiologists would recommend the need for a pre-procedure renal function test to ascertain that the kidney functioning is normal. This might delay the scan by a few hours. In patients who would need immediate scans or in those with deranged renal parameters a non-contrast CT scan can be performed to rapidly rule out hydrocephalus so that a lumbar puncture can be performed and microbiological analysis of the CSF done to ascertain the specific causative organism (Kastrup et al. 2008; Aiken 2010; Rangarajan et al. 2014).

Meningitis Imaging has a very low sensitivity in the diagnosis of meningitis. Thin continuous leptomeningeal enhancement may be seen along the convexity of the brain in cases of bacterial and viral meningitis. The presence of exudates in the basal cisterns is considered typical of tuberculosis. MRI easily differentiates basal cisternal enhancement from vessels in the region of the circle of Willis in a case of equivocal abnormal subarachnoid space enhancement on CT. Also, enhancement over the cerebral convexities is easier to appreciate on MRI as opposed to CT because the overlying inner table of the skull is seen as an adjacent signal void on MR imaging unlike in CT in which the bones show hyperdense signal resulting in decreased contrast difference between the meningeal enhancement and the bone. In a patient in whom contrast administration is not possible, a non-contrast MRI would provide more details than a non-contrast CT due to better contrast resolution at the expense of longer scan duration (Douglas et al. 2014; Mohan et al. 2012).

The main role of imaging in meningitis is to detect complications (Kastrup et al. 2008; Rangarajan et al. 2014; Mohan et al. 2012; Rath et al. 2012) (Fig. 19.5) which include

- Communicating hydrocephalus—due to impaired CSF absorption by inflammatory exudates. Leptomeningeal-ependymal fibrosis leading to irreversible communicating-obstructive hydrocephalus may follow bacterial meningitis
- Cerebritis
- Abscess
- Ventriculitis—a thin rim of ventricular enhancement

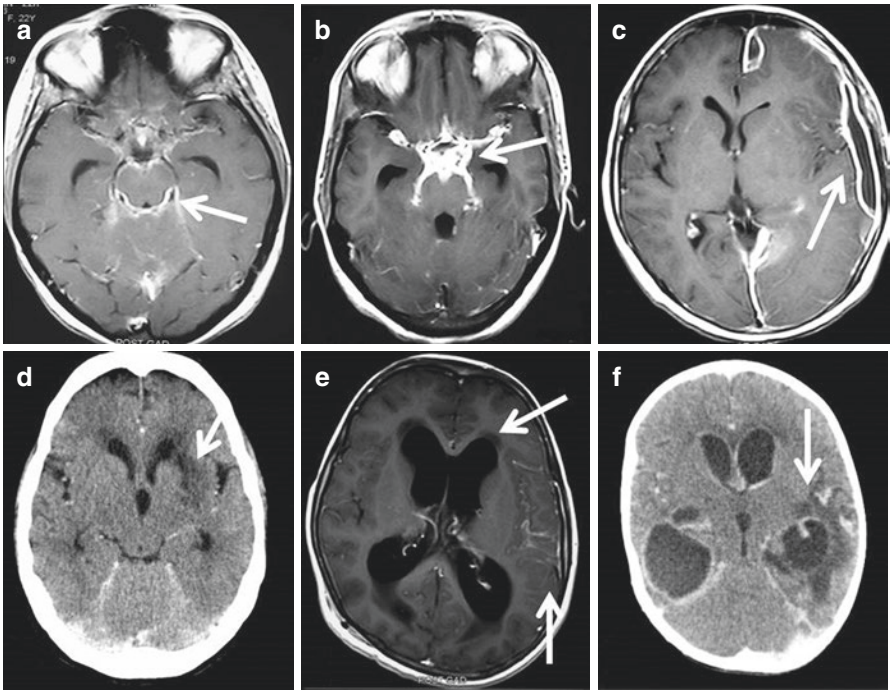

Fig. 19.5 Meningitis and its complications—Smooth leptomeningeal enhancement in bacterial meningitis (**a**), thick enhancing exudates in the basal cisterns in tubercular meningitis (**b**), smooth leptomeningeal enhancement with hydrocephalus (**c**), subdural fluid with smooth peripheral enhancement in subdural empyema (**d**), hypodensity in the left basal ganglia region with loss of gray–white matter differentiation due to development of infarct (**e**), smooth enhancement of the ventricular lining with periventricular hypodensity in ventriculitis secondary to rupture of bacterial abscess into the ventricle (**f**)

- Subdural effusion—irritation of the dura by the infectious agent or by its products. Or secondary to inflammation of the subdural veins with an associated increase in protein and fluid in the subdural space
- Subdural empyema
- Cortical/subcortical/basal ganglia infarcts—due to the involvement of perforating basal vessels by associated vasculitis (especially in tuberculosis)
- Venous infarcts—due to venous sinus thrombosis.

Cerebritis and Abscess Four pathological stages are described in the formation of an abscess each with distinct imaging features

- Early cerebritis stage—normal or poorly marginated cortical or subcortical edema and mass effect
- Late cerebritis stage—more defined, but still irregular, a rim-enhancing lesion with a hypodense center
- Early capsule stage—discrete lesion with thin enhancing rim and surrounding edema

- Late capsule stage—progressive central necrosis, cavity shrinks, decreasing surrounding edema

Usually, the diagnosis is made in the late cerebritis stage or early capsule stage. MRI is superior to CT due to its greater sensitivity to subtle parenchymal changes, like white matter changes. Also advanced techniques like MR spectroscopy help in the differentiation of bacterial/fungal/tubercular abscess (Rangarajan et al. 2014; Rath et al. 2012).

Encephalitis Infiltration of the parenchymal by inflammatory cells and is commonly due to a viral etiology. The brain damage is due to a combination of intracellular viral growth and the host inflammatory response. A few common viral encephalitides are described in detail below (Fig. 19.6).

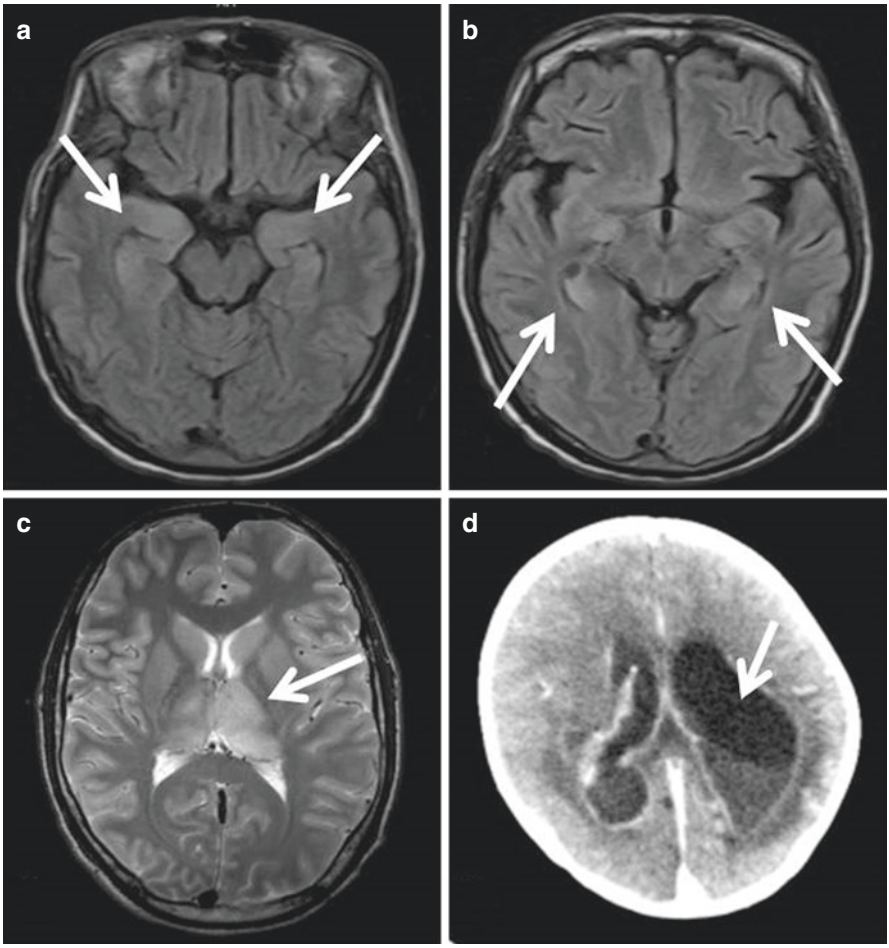

Fig. 19.6 Encephalitis—bilateral hippocampal hyperintensity in herpes encephalitis (**a**, **b**), bilateral asymmetric thalamic hyperintensity in Japanese encephalitis (**c**), smooth ependymal enhancement with debris in the ventricle in ventriculitis in CMV (**d**)

Herpes simplex encephalitis—HSV 1 is the cause in nearly 95% of the cases and is considered to be caused due to latent herpes simplex virus in the Gasserian ganglion, with retrograde spread along the trigeminal nerve to involve the temporal and inferior frontal lobes. This explains the predilection for the involvement of the limbic system (inferomedial temporal lobes, the orbital surface of the frontal lobes, and the insular cortex). Posterior occipital cortex, cerebral convexity, and the external capsule may also be involved with typical sparing of the basal ganglia. Involvement may initially be unilateral but is typically followed by less severe contralateral disease. This "sequential bilaterality" is highly suggestive of herpes encephalitis. Small petechial hemorrhages are often present. In immunocompromised patients, there may be multifocal involvement and may not conform to the typical imaging appearance (Rangarajan et al. 2014; Granerod et al. 2016; Bonnici-Mallia et al. 2016).

Varicella-zoster virus encephalitis usually presents as brainstem encephalitis due to spread along the V and VII cranial nerves to the brainstem. This may be accompanied by vasculitis.

Cytomegalovirus encephalitis is usually seen in immunocompromised patients and is characteristically accompanied by ependymitis. Post-contrast MRI reveals considerable enhancement along the ependyma (Rangarajan et al. 2014; Mohan et al. 2012; Rath et al. 2012).

Japanese encephalitis (JE) presents with characteristic neurologic findings during the acute stage like extrapyramidal signs such as tremor, dystonia, and rigidity. JE should be distinguished from other types of encephalitis, particularly HSE, because antiviral therapy for HSE is very effective in the acute stage while specific antiviral therapy is not available for JE, its treatment being supportive. JE shows diffuse meningoencephalitis affecting both gray and white matter of the cerebral hemispheres, basal ganglia, brainstem, cerebellum, and thalamus (Rangarajan et al. 2014; Basumatary et al. 2013; Misra et al. 2003).

Other infections include cryptococcosis, toxoplasmosis, neurocysticercosis, and various other viral infections which are beyond the scope of discussion in the chapter.

Demyelination (including both Acute Demyelinating Encephalomyelitis (ADEM) and Multiple sclerosis) is a great mimicker with a wide range of imaging appearances. Typical white matter involvement with sparing of gray matter are subtle signs to help in the differentiation from infective pathology, although a definitive distinction may not be possible always based on imaging and would need correlation with clinical features and microbiological and pathological analysis of the CSF (Rangarajan et al. 2014; Ketelslegers et al. 2010).

19.3 Abdomen

Infections in the abdomen in the ICU setting can be grouped into hepatobiliary, gastrointestinal, genitourinary, and peritoneal causes as enlisted below.

1. Hepatobiliary
   - Liver abscess
   - Cholangitis

- Emphysematous cholecystitis
- Infected pancreatic collections
- Splenic abscess

2. Gastrointestinal
   - Infective enterocolitis and related complications
   - Intestinal perforations
   - Post-op leaks
3. Genitourinary
   - Pyelonephritis
   - Cystitis
   - Prostatitis, Prostatic abscess
   - Endometritis, Salpingo-oophoritis
   - Tubo-ovarian abscess
4. Peritoneal
   - Spontaneous bacterial peritonitis
   - Secondary peritonitis

Septic shock and acute kidney injury are more common in abdominal infections than with infections in other sites. And there is a greater degree of diversity in the causative organism than other organ systems. Hence an accurate and timely diagnosis is imperative to improve clinical outcomes (Shirah and O'Neill 2014).

Although radiology does not help in identifying the exact etiology of intra-abdominal infection, it can be helpful to narrow down on the organ system and to decide upon further treatment strategies (Fig. 19.7).

Gastrointestinal —In a suspected case of bowel obstruction or perforation, plain x-rays can demonstrate free air in the setting of perforation, pneumatosis in the setting of ischemic bowel, or abnormally dilated loops of bowel in the setting of toxic megacolon or bowel obstruction. In a relatively stable patient in the subacute or post-op setting, contrast studies may be used to reveal fistulas or leakage from a perforated hollow viscus or anastomotic leaks. However, CT scan with IV contrast helps in diagnosing luminal and extraluminal pathology as well as to look in hidden areas that may not be seen with ultrasound especially in the post-op setting due to a limited acoustic window (Paulson and Thompson 2015; Jaffe and Thompson 2015; Suri et al. 1999).

Hepatobiliary Ultrasonography can be a highly useful tool to localize the infections in case of hepatobiliary or genitourinary causes. It helps in assessing the solid organs for abscesses or granulomas, assessing the biliary tract in patients with obstructive jaundice or for assessing intra-abdominal collections or free fluid (in cases of peritonitis) with good diagnostic accuracy in experienced hands. Also, it can be used for guided aspiration to improve the diagnostic yield. When cross-sectional imaging is to be used, CT with IV contrast is used to look for complications and other associated findings, while MRI with MRCP (magnetic resonance cholangiopancreatography) is better to assess the biliary tree. CT also has higher sensitivity in detecting complicated pancreatic collections and also helps in CT guided drainage procedures in infected pancreatic collections (Dhaka et al. 2015; Morgan et al. 1997).

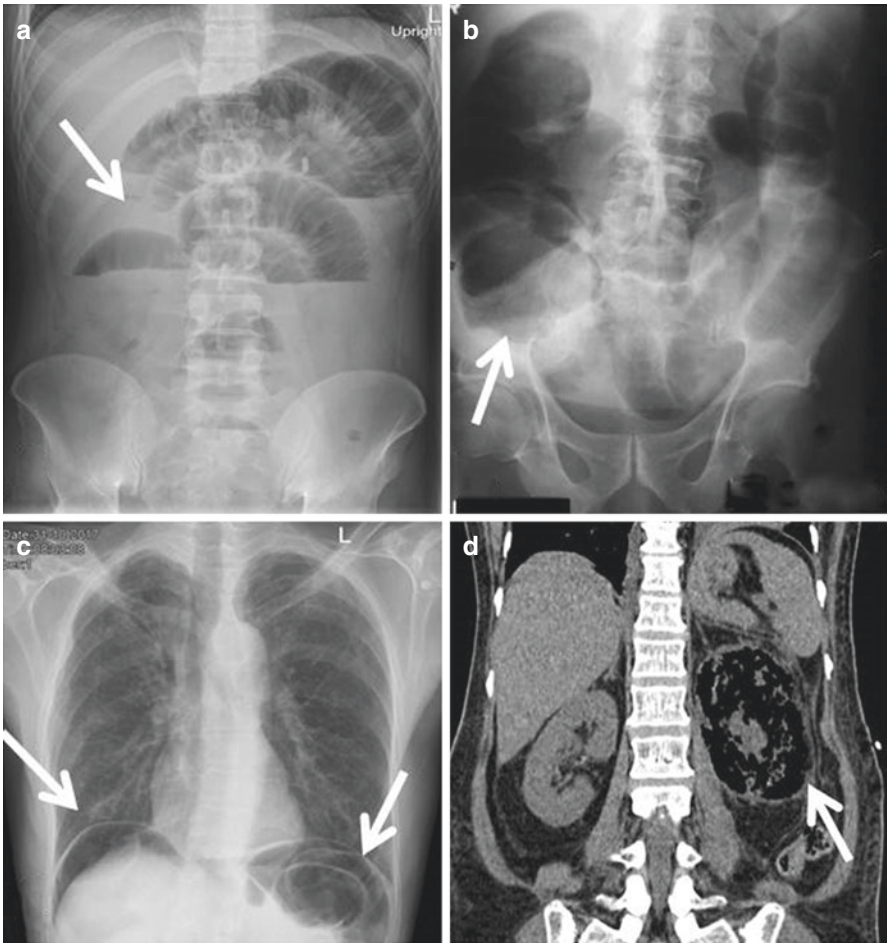

Fig. 19.7 Abdominal Pathologies—Small bowel obstruction with dilated small bowel loops and multiple air-fluid levels (**a**), large bowel obstruction with dilated large bowel loops and absence of rectal air (**b**), pneumoperitoneum on chest radiograph (**c**), coronal CT showing air in the left renal fossa in emphysematous pyelonephritis (**d**)

Genitourinary Uncomplicated UTI does not warrant further imaging and is usually confirmed by urinalysis. However, in complicated cases, cross-sectional imaging is used to look for complications like perinephric collections/emphysematous pyelonephritis.

Endocavitary probes for Trans-vaginal ultrasound or Trans-rectal ultrasound examination in cases of suspected genital infection improve the diagnostic accuracy although a transabdominal ultrasound of the pelvis using bladder as acoustic window also gives reasonably good results in detecting the genitourinary pathologies

and pelvic collections. CT may be required in certain cases when the extent of the disease cannot be ascertained on USG (Laing 1992).

Peritoneal Usually present with free fluid or collections in the peritoneal cavity, ultrasound-guided aspiration of which would help in diagnosing the cause and the specific organism.

19.4 Miscellaneous Infections

Other sources of infections can be the extremities in the form of cellulitis and their complications. USG is used in such cases to rule out complications like abscess formation. Bone involvement by infections is rare in the ICU setting, although rarely acute osteomyelitis and septic arthritis may be seen in the pediatric population. Infections of the extracranial head and neck usually require ENT examination along with ultrasound and CT with IV contrast for identifying various complications like a retropharyngeal abscess.

19.5 Role of Interventional Radiology

As discussed above image-guided interventions play a crucial role in the management of various infections. Ultrasound-guided procedures can be done at the bedside while fluoroscopy and CT guided procedures need shifting of the patient to the radiology department. Various procedures that can be done include -

- Diagnostic aspiration—using 18G or 20G needles for pleural, peritoneal, abdominal, and pelvic collections.
- Diagnostic sampling (biopsy)—CT guided biopsy is done for certain lung infections that do not respond to empirical therapy.
- Therapeutic aspiration—usually USG guided Pigtail insertion (8-12F) using either a single puncture or Seldinger technique with graded dilators. CT guidance used for pancreatic collections and some pelvic collections.
- Biliary drainage (Percutaneous Transhepatic Biliary Drainage—PTBD)—in cholangitis when an endoscopic procedure cannot be done or has failed.
- Urinary drainage (Percutaneous Nephrostomy—PCN)—in complicated UTI like pyonephrosis.
- Vascular interventions—complications of infections like pseudoaneurysms can be managed with endovascular embolization.

Thus radiology plays an important role in the management of infections in the ICU setting and its optimal usage would enable us to localize, diagnose, and treat some of the complications in a timely and minimally invasive manner improving the overall clinical outcomes.

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Selection of Antibiotics in Infectious Diseases in the Critically Ill

20

Puneet Khanna and Shyam Madabhushi

20.1 Malaria

Sevevalaria is an important cause of morbidity and mortality, especially in tropical countries and in travelers returning from endemic areas. Patients presenting to the ICU usually have severe malaria. Despite adequate therapy, mortality rate remains around 10–20%. Treatment should be initiated on suspicion alone of Malaria.

WHO guidelines (World Health Organization 2019) emphasize the superiority of artemisinin derivatives over quinine, based on studies in Asia and Africa (Dondorp et al. 2005; White et al. 2014). Parenteral therapy is recommended for at least 24 h, and a full dose of ACT (Artemisinin Combination Therapy) should be given after the first 24 h and when the patient is able to tolerate oral therapy. Artemether is another parenteral alternative to artesunate. Quinine must be used only when artemisinin derivatives are unavailable.

Empirical broad-spectrum antibiotics also must be started. Although case series from Africa suggest *Salmonella* species as an important aetiological agent, this recommendation cannot be universal. Healthcare associated infections like VAP and CRBSI should be considered in ICU patients.

Typical doses of antimalarial drugs are as follows (Cheng and Yansouni 2013).

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Drug	Dose	Frequency and special instructions
Artesunate	2.4 mg/kg per dose	0, 12, and 24 h, thereafter daily. No adjustment needed for hepatic or renal dysfunction
Quinine	Load: 20 mg/kg of salt over 4 h- followed by 10 mg/kg of salt 8 h after the start of the loading dose given over 2–4 h	10 mg/kg salt given over 2–4 h, every eighth hourly Monitor ECG for QT prolongation. Max infusion rate 5 mg/kg salt per h. Hypoglycaemia from islet cell stimulation. Administer with D5W or run dextrose infusion separately
Artemether	Initial dose: 3.2 mg/kg IM in the anterior thigh	Maintenance: 1.6 mg/kg IM daily. Available as an oily preparation

If oral therapy is not feasible after the initial 24 h (therefore ACT not feasible), Artesunate must be combined with either Doxycycline or Clindamycin. This combination is especially important in endemic countries like India.

ACT options are listed below. However, in patients with suspicion of cerebral malaria, ACT preparations containing Mefloquine must be avoided due to an increased risk of neuropsychiatric symptoms. The duration of ACT is 3 days (covers two sexual cycles).

Drug combination	Dose range	Remarks
Artemether-Lumefantrine	Total 3-day dose: 5–24 mg/kg of Artemether and 29–144 mg/kg Lumefantrine	Dosed as twice a day, for 3 days; the first two doses ideally must be 8 h apart
Artesunate-Amodiaquine	2–10 mg/kg per day of Artesunate and 7.5–15 mg/kg per day Amodiaquine	Dosed as once daily for 3 days
Artesunate-Mefloquine	Artesunate 2–10 mg/kg per day, Mefloquine 5–11 mg/kg per day	Dosed as once daily for 3 days. Mefloquine not to be used in suspected cerebral malaria
Artesunate + Sulfadoxine-Pyrimethamine (SP)	Artesunate 2–10 mg/kg per day; SP Artesunate 2–10 mg/kg per day; 25–70 mg/kg Sulfadoxine and 1.25–3.5 mg/kg Pyrimethamine	Artesunate dosed once daily for 3 days; SP administered as a single dose ONLY ON DAY 1.
Dihydroartemisinin-Piperaquine	2–10 mg/kg per day Dihydroartemisinin and 16–27 mg/kg per day Piperaquine	Dosed as once daily for 3 days

The latest report on ACT drug resistance (Global Malaria Programme 2018) suggests that in India, there is a risk of treatment failure >10% with the Artesunate-SP combination, and therefore, Artemether-Lumefantrine is the preferred combination, especially in the north-eastern region of the country.

20.2 Typhoid

Patients suspected or proven to have invasive Salmonellosis are admitted to the ICU in cases of severe disease with multiorgan dysfunction. The index of suspicion for a typhoidal illness must be high in order to initiate therapy early.

Drug choices for severe typhoid must account for drug resistance, an important problem in the SE Asian region. The API guidelines (Upadhyay et al. 2015) suggest that fluoroquinolones (esp Ciprofloxacin and Ofloxacin) and Cephalosporins (esp third and fourth generation) are the first-line therapeutic options. However, a study conducted in many countries of SE Asia (Barkume et al. 2018) revealed a > 80% resistance to fluoroquinolones. Given this data, fluoroquinolones cannot be recommended as first-line therapy in severe disease. Further, a report from Pakistan (Klemm et al. 2018) suggests that starting in 2016, a plasmid-mediated, extensively drug resistant (XDR) strain of typhoid has been responsible for more than 300 cases in Sindh, with one case of travel-related XDR case mediated by the same plasmid in the UK. The impact of this on treatment choices in India is not clear.

For initial therapy, parenteral antibiotics are recommended. Current guidelines (Upadhyay et al. 2015) recommend monotherapy. The choices, keeping in view the resistance patterns, may be summarized as follows:

Drug	Dose	Duration
Ceftriaxone	60–75 mg/kg per day	14 days
Cefotaxime	80 mg/kg per day	14 days

In case of non-response (lack of defervescence by D5), combination therapy may be used. Since India falls in the area of high fluoroquinolone resistance, Azithromycin may be recommended. Data backing this approach is not robust. The dose of azithromycin is 20 mg/kg per day orally, to a maximum of 1000 mg. The recommended duration for Azithromycin is 7 days.

The addition of corticosteroids to antibiotics in severe disease rests on data from an early study in Indonesia, published in 1984 (Hoffman et al. 1984), which suggested a reduction in mortality in severe disease (delirium, obtundation, stupor, coma or shock) with the use of high dose dexamethasone (3 mg/kg). However, the antibiotic used was Chloramphenicol, which is not commonly used today. The role of steroids with current antibiotic classes has not been evaluated.

If XDR is suspected, Meropenem is the choice of agent for severe disease (XDR strain remains susceptible to Carbapenems and Azithromycin). The recommended dose is 20–40 mg/kg per dose, administered every 8 h.

20.3 Rickettsial Diseases

Scrub typhus is a rickettsial disease endemic to many states and regions in India, and its incidence is increasing. Diagnosing the disease is difficult because of the protean manifestations. Untreated disease has a mortality of at least 30–45% (Batra 2007; Rathi and Rathi 2010). The DHR-ICMR guidelines (Rahi et al. 2015) cover scrub typhus, murine typhus, and Indian tick typhus. However, the evidence base for these guidelines is not backed up by high-quality data. A Cochrane review of antibiotics for treating scrub typhus published in 2018 (El Sayed et al. 2018) highlighted that the GRADE certainty of the evidence was low to very low. Four antibiotics were identified as being effective against Scrub typhus: Tetracycline,

Doxycycline, Rifampicin, and Azithromycin. Chloramphenicol was also considered, but could not be included. There was no definite evidence for superiority of Tetracyclines vs Azithromycin.

In all critically ill patients, intravenous therapy is recommended initially, which may be converted to oral therapy as the clinical condition improves.

The recommended antibiotics for scrub typhus are:

Drug	Dose	Duration
Doxycycline	100 mg twice daily	IV therapy initially, thereafter oral therapy in the same dose for 7–15 days
Azithromycin	500 mg IV once daily	IV therapy for the first 24–48 h, followed by oral therapy for a total of 5 days

If there is no response to treatment with Doxycycline, the strain may be considered resistant to it, and Azithromycin may be used. However, these preferences have not been reflected in clinical trials.

20.4 Leptospirosis

Leptospirosis is a zoonoses caused by a spirochete. Manifestations are protean, with multiorgan failure and death in severe cases. Patients with severe disease are admitted to the ICU for management.

Treatment choices (NCDC 2015) for severe disease are usually beta-lactams. The preferred agents are:

Drug	Dose	Duration
Crystalline or Benzylpenicillin	20 lakh IU every 6-hourly, or 30 mg/kg IV 6-hourly respectively	7 days
Ceftriaxone	1–2 g IV once a day	7 days
Cefotaxime	1 g IV 6-hourly	7 days
Doxycycline	100 mg IV 12-hourly	7 days

Penicillin is the drug of choice in severe disease. Ceftriaxone or Cefotaxime may be administered in case of allergy to Penicillin. Doxycycline, although listed here, is preferred for mild disease. The advantage of doxycycline is that is the drug of choice as well for other tropical diseases like Scrub typhus. In the initial stages of undifferentiated tropical illness, it may be a good choice, with a switch to Penicillin when the diagnosis of Leptospirosis is achieved.

20.5 Community Acquired Meningitis

Bacterial meningitis is a medical emergency. Empirical antibiotic therapy must be initiated at the earliest, pending culture results. If for some reason lumbar puncture is likely to be delayed, blood cultures must be obtained and intravenous antibiotics must be promptly administered.

The causal organism must be guessed initially based on patient and epidemiological characteristics. In otherwise healthy adults, the dominant organism is *S pneumoniae*, although the rates at which this organism is isolated varies with geography. The ESCMID guidelines (van de Beek et al. 2016) report the pooled incidence of *S pneumoniae* to be around 53% and *N meningitidis* to be 27%. The data from India (Chandramuki et al. 2007) suggest that a causal organism could be identified in 73.8% of cases, with *S pneumoniae* being isolated in 61.8% of cases, while *N meningitidis* was identified in 1% of the cases. The rates of pneumococcal resistance in this study to ceftriaxone was 6.8%. Recent data from a hospital-based sentinel surveillance in children (Jayaraman et al. 2018) obtained in 2012–2013 indicated Pneumococcal sensitivity to cefotaxime to be around 93%, while the corresponding figure for Penicillin was 86%. All isolates were resistant to Cotrimoxazole. In elderly individuals, Listeria Monocytogenes is an important pathogen. All antibiotics must be administered intravenously.

For community acquired bacterial meningitis, the following empirical therapy is recommended(van de Beek et al. 2016):

Age	Drug	Dose	Duration
>18 year and <50 year	Ceftriaxone + Vancomycin	2 g 12hourly + 10-20 mg/kg 8–12hourly	10–14 days
>50 year, or patients with risk factors for *L monocyogenes*	Ceftriaxone + Vancomycin+ Amoxycillin	2 g 12hrly + 10-20 mg/kg 8-12hourly+ 2 g 4-hourly	10–14 days

Risk factors for Listeria include Diabetes Mellitus, use of immunosuppressive drugs, and other conditions causing immunocompromise.

Although the addition of Rifampicin is suggested, this is not a practical approach in India as the use of Rifampicin for non-tubercular infections will add to the risk of increasing the incidence of MDR/XDR TB. Once the causal organism is isolated, culture-specific antibiotics must be administered in their full doses. Steroids must be used as per standard indications.

20.6 Community Acquired Pneumonia

The subset of patients admitted to the ICU with CAP have severe pneumonia. Empirical therapy in this subset of patients must cover likely pathogens.

The main obstacle in choosing antibiotics for CAP in India is lack of epidemiological data. In addition, the rates of culture positivity are very low, for example, in the study by Song et al. (Song et al. 2008), a causal pathogen was identified in only 45%.

Some Indian data have to be put into perspective for understanding the causal agents in CAP. 225 patients were enrolled in a study published in a north Indian hospital (Para et al. 2018). Streptococcus pneumoniae was isolated in 30.5% of the

patients, while Legionella was seen in 17.5%. Mycoplasma and Chlamydia combined account for 12.7% of cases. Klebsiella pneumoniae was isolated in 4.8%, while MRSA was seen in 1.7%. In a study in Southern India (Prasad and Bhat 2017), the common isolates were Klebsiella pneumoniae (29.09%) and Pseudomonas (18.18%). S pneumoniae was isolated in 13.33% of patients. The overall culture positivity rate was 48%.

Keeping in mind this data, empirical antibiotic choice must be based depending on the most likely pathogens. Classification systems and risk factors have been identified that are capable of identifying the likelihood of MDR organisms causing CAP.

The ISCCM guidelines identify risk factors (Gc et al. 2019) for MDR organisms. These are:

- Age >65 year.
- Antimicrobial therapy in the preceding 3 months.
- High frequency of antimicrobial resistance in the community.
- Hospitalization for >48 h in the preceding 3 month
- Home infusion therapy including antibiotics
- Home wound care
- Chronic dialysis within 1 month
- Family member with MDR pathogen
- Ongoing immunosuppression

Risk factors for Pseudomonas include:

- Chronic pulmonary disease (COPD, bronchial asthma, bronchiectasis)
- Frequent systemic corticosteroid use
- Prior antibiotic therapy
- Old age
- Immunocompromised states
- Enteral tube feeding
- Cerebrovascular or cardiovascular disease

Risk factors for MRSA in CAP in the ICU include:

- Close contact with MRSA carrier or patient
- Influenza
- Prisoners
- Professional athletes
- Army recruits
- Men having sex with men
- IV drug abusers
- Regular sauna users
- Those with recent antibiotic use
- Cavitation or necrotising pneumonia

Risk factors for aspiration in patients admitted for CAP in the ICU are:

- Dysphagia
- Altered sensorium
- Coma
- Witnessed aspiration
- Putrid discharge
- Presence of lung abscess
- Empyema
- Necrotising pneumonia

These risk factors are similar to those in the IDSA/ATS guidelines for CAP (Mandell et al. 2007). These guidelines are now in the process of being revised.

The choices, accordingly are

1. For patients without MDR risk factors, the options are:
   (a) A potent, non-pseudomonal beta-lactam (Cefotaxime, Ceftriaxone, Amoxycillin-Clavulanate) PLUS a macrolide (Azithromycin, Clarithromycin).
   (b) A potent, non-pseudomonal beta-lactam (Cefotaxime, Ceftriaxone, Amoxycillin-Clavulanate) PLUS a respiratory fluoroquinolone (Levofloxacin, Moxifloxacin, Ciprofloxacin). In India, fluoroquinolones are second-line agents for TB. Therefore, this option should be used ONLY if macrolides cannot be used. In this case, a sputum sample must be sent for AFB detection and nested PCR detection for mycobacteria (GeneXpert).
   (c) In case of penicillin allergy, Aztreonam PLUS a respiratory fluoroquinolone (Levofloxacin, Moxifloxacin, Ciprofloxacin) must be used. The caveats in 1(b) above apply.
2. In patients in whom Pseudomonas is a risk factor, the following choices apply:
   (a) An anti-pneumococcal, anti-pseudomonal beta-lactam (Piperacillin-Tazobactam, Cefepime, Ceftazidime, Cefoperazone-Sulbactam, Imipenem, Meropenem) PLUS an anti-pseudomonal fluoroquinolone (Ciprofloxacin, Levofloxacin).
      - Ciprofloxacin is more active against Pseudomonas than Levofloxacin.
   (b) An anti-pneumococcal, anti-pseudomonal beta-lactam (Piperacillin-Tazobactam, Cefepime, Ceftazidime, Cefoperazone-Sulbactam, Imipenem, Meropenem) PLUS an Aminoglycoside (Amikacin, Gentamicin) PLUS Azithromycin.
   (c) An anti-pneumococcal, anti-pseudomonal beta-lactam (Piperacillin-Tazobactam, Cefepime, Ceftazidime, Cefoperazone-Sulbactam, Imipenem, Meropenem) PLUS an anti-pseudomonal fluoroquinolone (Ciprofloxacin, Levofloxacin) PLUS an Aminoglycoside (Amikacin, Gentamicin).
      - For Penicillin-allergic patients, substitute Aztreonam for beta-lactam.
3. In patients with risk factors for MRSA:
   (a) Add Vancomycin or Linezolid to the beta-lactam.
4. For patients with suspected aspiration-related pneumonia, any of the following are effective:

(a) Amoxycillin-clavulanate.
(b) Ampicillin and Metronidazole.
(c) Clindamycin.
(d) Ceftriaxone PLUS Metronidazole.
(e) If patient is already on any of the following, additional anaerobic coverage is not indicated.
    - Imipenem
    - Meropenem
    - Piperacillin-Tazobactam

The duration of therapy for CAP is:

- 7–10 days for CAP
- 14 days for Pseudomonas and pneumonia due to aspiration
- 14–21 days for necrotising pneumonia due to GNB, MRSA, and anaerobes.

20.7 Skin and Soft Tissue Infections (SSTIs)

SSTIs are a heterogenous group of disorders, with involvement of skin, skin structures, and underlying soft tissues. The organism responsible is variable, depending on the site of infection. Although a majority of these infections can be managed either on an OPD or ward basis, they sometimes can lead to severe systemic derangements with multiorgan failure, and need ICU care.

The potential organisms involved (Burnham et al. 2016) in SSTIs are Staphylococcus aureus, Streptococcus pyogenes, and beta-hemolytic streptococci. In certain defined entities like Ecthyma gangrenosum, Pseudomonas aeruginosa is responsible. GNB Enterobacteriaceae are involved in infections involving the pelvis and lower limb. Clostridial species are a concern in gas gangrene and myonecrosis, while necrotising fasciitis is usually polymicrobial.

Antimicrobial choices in SSTIs are reflective of the site and putative organisms involved. The IDSA guidelines on the management of SSTIs (Stevens et al. 2014) primarily categorize SSTIs into "purulent" and "non-purulent" categories. Purulent infections include furuncles, carbuncles, and abscesses, while non-purulent infections include Necrotising fasciitis, cellulitis, etc. However, these classifications are arbitrary, and clinical judgement is warranted.

Purulent infections are treated using antibiotics effective against Staphylococcus, with concern for MRSA. Severe non-necrotising infections are treated by a combination of antibiotics against Gram-negative bacilli, specifically Pseudomonas, and MRSA. These choices are reflected in the table below.

Type of infection	Antimicrobial choice
Severe, non-necrotising infection	Vancomycin + Piperacillin-Tazobactam/ Imipenem
Severe, purulent infection (abscess, carbuncle, furuncle)	Vancomycin OR Daptomycin OR linezolid
Clostridial infection/Streptococcus pyogenes	Penicillin PLUS clindamycin

Clindamycin, in itself, has no anti-MRSA activity, and therefore must not be used when there is a concern for MRSA. It is also to be noted that SSTIs frequently need surgical drainage, and more than one session may be necessary. The usual duration of antibiotic therapy is 5–7 days in uncomplicated SSTIs. Complicated SSTIs may necessitate therapy for 10 days.

20.8 Biliary Sepsis

Biliary sepsis is usually the result of an obstructed biliary system or due to instrumentation of the biliary tract. The obstruction may be benign, malignant or iatrogenic. The microbiology of biliary sepsis is polymicrobial. Gram-negative organisms dominate (Miura et al. 2018), with E coli being the most common, followed by Klebsiella and Enterobacter. These are usually of gut origin. Gram-positive Enterococcus is also involved. Bacteroides and Clostridial species are also involved (part of gut flora), but are difficult to culture (anaerobic), and have to be accounted for empirically.

Antibiotic choices have to cover all organisms involved, i.e., enteric streptococci, coliforms, and anaerobes. If the infection is healthcare-acquired, resistant bacteria are to be expected. For non-healthcare-related biliary sepsis, a combination of beta-lactam/beta-lactamase-inhibitor (BL-BLI) and metronidazole is suggested. Examples of such combinations are Cefoperazone-Sulbactam PLUS Metronidazole and Piperacillin-Tazobactam PLUS Metronidazole. Alternatives for patients allergic to beta-lactams are combinations of Fluoroquinolones (Ciprofloxacin, Moxifloxacin, Levofloxacin) with metronidazole. For healthcare-related biliary sepsis, a potent third- or fourth-generation BL/BLI or Carbapenem with Metronidazole PLUS Vancomycin is recommended. This spectrum intends to cover all possible organisms involved. It is to be noted that surgical or endoscopic intervention to decompress the biliary system is needed for successful management in an obstructed system. Cultures from infected bile, stones, or recovered stents can aid in narrowing the drug spectrum. However, it is reiterated that anaerobic cultures are seldom successful, and therefore, must be accounted for empirically.

20.9 Peritonitis

Peritonitis is a life-threatening condition, whose onset may be quite insidious, with the patient reporting to the healthcare facility after a considerable delay. This is especially true in secondary peritonitis from a lower GI/colonic perforation. Since there is no leakage of gastric acid into the peritoneal cavity, symptom onset is relatively delayed.

Peritonitis may be classified as primary, secondary, tertiary. In secondary and tertiary peritonitis, there is a breach in the integrity of the GIT, while in primary peritonitis, there is no apparent breach. Tertiary peritonitis is usually healthcare-related, with MDR organisms involved.

Microbiology of peritonitis is quite similar to biliary sepsis (Gc et al. 2019), with organisms of enteric origin predominating. Gram-negative coliforms like E coli are the most common. Enterococcus and anaerobic organisms are also involved, especially in secondary and tertiary peritonitis.

In primary peritonitis, e.g., that occurring in the setting of liver cirrhosis, monotherapy with a potent third-generation cephalosporin is usually considered adequate. Examples are Ceftriaxone and Cefotaxime. In secondary peritonitis, a BL-BLI or a Carbapenem in combination with Metronidazole is recommended. Examples are Cefoperazone-Sulbactam or Piperacillin-Tazobactam or Imipenem/Meropenem in combination with metronidazole. In tertiary peritonitis, or in secondary peritonitis with inadequate response, the addition of Vancomycin may be considered. The addition of antifungal agents (caspofungin, Amphotericin B) must be considered on an individual basis, especially in patients with non-resolving sepsis and septic shock.

The duration of recommended therapy is 7 days. Short courses of 4 days may also be considered in selected cases.

20.10 Management of Urosepsis

The causative organisms in urosepsis are usually gut-derived. E coli is the most common organism. Other Enterobacteriaceae, Pseudomonas, enterococci, and staphylococci are also causal organisms. This set of organisms is notorious for being multi-drug resistant (Bonkat et al. 2019).

The initial drug therapy in patients with urosepsis depends on the site of management, which in turn depends on patient severity. Patients admitted to the ward with features of UTI may be managed with a single antibiotic predominantly covering enteric GNB. However, patients who are in the ICU due to septic shock, or severe physiological derangements owing to urological sepsis need broader spectrum coverage to account for Extended Spectrum beta-lactamase producing organisms. Imipenem-Cilastatin, Meropenem, and Doripenem are the available choices. The decision to administer concurrent antibiotics against Gram-positive organisms is controversial. Suggested antibiotics are Vancomycin, Daptomycin, and Linezolid.

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Management of Gram Negative Multi-Drug Resistant Organisms in Intensive Care Units

21

Nitin Gupta and Manish Soneja

21.1 Introduction

Gram negative infections are responsible for causing infections in both community and healthcare settings (Gaynes and Edwards 2005). The proportion of infections caused by resistant gram negative organisms has been steadily increasing in recent times, more so in the hospitalized patients. Resistant gram negative organisms are one of the most difficult organisms to treat in intensive care units (Guervil and Chau 2013). Resistance to commonly used empiric antimicrobials leads to significant delay in response and therefore, infection with resistant organisms are associated with high mortality and morbidity. Increasing resistance complicates the decision making process with regard to the choice of empiric regimen. Indiscriminate use of broad spectrum antibiotics further increases the prevalence of resistance in these organisms, creating a vicious circle. In this chapter, the approach to diagnosis and management of gram negative organisms in intensive care unit has been discussed in an evidence informed manner (Fig. 21.1).

21.2 Epidemiology of Resistance in Gram Negative Organisms

The prevalence and mechanism of resistance in gram negative organism vary with the organism and geographical region. The mechanism of resistance in gram negative bacteria varies from enzyme production to target modification and efflux pumps. Beta-lactamase production is the most common mechanism of resistance in

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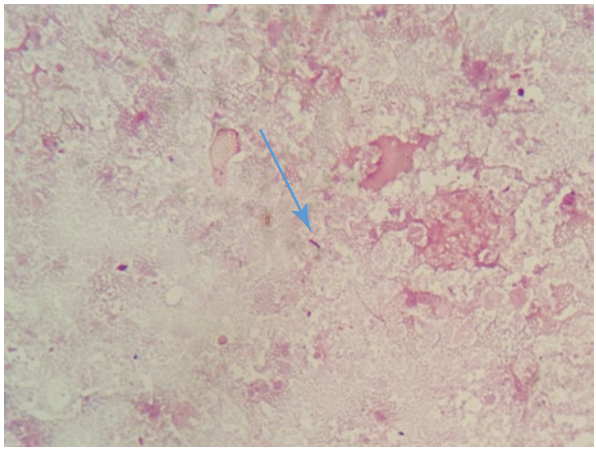

Fig. 21.1 Endotracheal aspirate showing gram negative bacilli in the center

Table 21.1 Common mechanisms of resistance in gram negative organisms (Ruppé et al. 2015)

	Extended spectrum B-lactamase (ESBL)				Carbapenemase		
B-Lactamase	Classical	CTX-M	OXA	AmpC	Class A	Class D	MBL
Examples	TEM 3, SHV-2		11, 14, 15, 16,17		*KPC*, SME, IMI	OXA 23, 24, 40, 51, 58	*NDM*, IMP, VIM
Genetics	Pla	Pla	Pla	Chr > Pla	KPC-Pla	51-chr Others-Pla	NDM-plasmid IMP/VIM-Chr
Organisms	Eae	Eae	Pae	SPICE, aba, rarely Pae	Eae, Pae	Aba	Eae, aba
4G Cephalosporins	R	R	R	?S	R	R	R
Cephamycins	S	S	S	R	R	R	R
Monobactams	R	R	R	R	R	R	?S
Carbapenems	S	S	S	S	R	R	R
Clavulunate/ Tazobactam	S	S	R	R	?S	R	R

Pla Plasmid mediated, *Chr* Chromosomal mediated, *Eae* Enterobacteriaceae, *Pae* Pseudomonas, *Aba* Acinetobacter, *SPICE* Serratia, Providencia, Indole positive Proteus, Citrobacter, Enterobacter

most organisms. The classification of beta-lactamases is based on either molecular structure (Ambler classification) or functional similarities (Bush-Jacoby classification) (Hall and Barlow 2005), (Bush and Jacoby 2010). However, for simplification, the common beta-lactamase classes that are clinically relevant are only discussed here—Extended spectrum beta-lactamase (ESBL), AmpC, and Carbapenemase (Table 21.1).

The major causes of resistance to third-generation cephalosporins in Enterobacteriaceae are due to production of ESBL or AmpC enzymes (Ruppé et al. 2015). The common carbapenemases observed in the Enterobacteriaceae are Klebsiella producing carbapenemase—KPC (more common in USA and Europe), New Delhi Metallo-beta-lactamase—NDM (more common in India and neighboring countries) and carbapenem-hydrolyzing oxacillinases—OXA. In the case of *P. aeruginosa* and *A. baumannii*, resistance is usually due to either a combination of different mechanisms, including b-lactamase production, increased efflux pump activity, and outer membrane modifications or to a single potent resistance mechanism such as carbapenemase production (Ruppé et al. 2015). Carbapenem resistance in *A. baumannii* is primarily mediated by OXA enzymes. With increasing use of polymyxins to treat carbapenem resistant gram negative organisms, resistance to polymyxins (commonly due to plasmid mediated mcr-1 gene) have also emerged (Srinivas and Rivard 2017).

21.3 Clinical Features, Diagnosis and Treatment

The clinical features and diagnostic strategies vary according to the site of infection and presence or absence of secondary bacteremia and sepsis/septic shock. The most common syndromes associated with gram negative infections have been summarized in Table 21.2.

While chhosing an empiric antimicrobial for patients with suspected gram negative infection, the following four questions should be taken into account; i) What is the syndromic diagnosis, ii) Whether the patient is in shock or is critically ill, iii) Which gram negative bugs are you suspecting and, iv) Are there any risk factors for resistance. Empiric antimicrobial therapy for gram negative organism has to be guided by the local resistance patterns and the hospital antibiogram. Clinical condition of the patient, presence of shock, underlying co-morbidities, prior antibiotic use, presence of indwelling catheters, and history of hospitalization has to be taken into account. In cases with sepsis/septic shock or presence of risk factors for MDR (immunocompromised host, recent healthcare exposure, high prevalence of MDR organisms in the institute), the therapy has to be more aggressive and needs to have an anti-pseudomonal coverage (Bassetti et al. 2017). Anti-pseudomonal agents include piperacillin/tazobactam, cefepime, ceftazidime, aztreonam, imipenem, meropenem, ciprofloxacin, levofloxacin, gentamicin, amikacin, and polymyxins (Giamarellou and Antoniadou 2001).

The important clinical trials that have helped in revolutionizing the treatment of MDR GN organisms are summarized in Table 21.3.

For patients with infections caused by ESBL producing gram negative bacteria, carbapenems are the treatment of choice. The use of beta-lactam-beta-lactamase inhibitor combinations (BL/BLI) as an alternative to carbapenems has been demonstrated in some studies but other studies have shown contradicting results. It appears that BL/BLI may be used in patients with urinary tract infections due to higher concentration of the antimicrobials in urine but carbapenem is still the preferred choice

Table 21.2 Clinical syndromes associated with gram negative infections (Stryjewski and Boucher 2009; Kalil et al. 2016; Nair and Niederman 2013; Vásquez et al. 2017)

Clinical syndrome	Common microorganisms	Clinical features	Diagnosis	Treatment
Bacteremia	Community acquired—*Escherichia coli* (most common) Hospital acquired—*Pseudomonas aeruginosa, Klebsiella pneumoniae, Escherichia coli*	Fever, shaking chills, features of sepsis. Usually secondary to infection at other site (e.g. community acquired bacteremia is usually secondary to UTI)	Blood culture (plus catheter tip in CLABSI) Rapid diagnostic tests such as MALDI-TOF and multiplex PCR can be used	Sepsis/ septic shock + risk features of MDR—Two anti-pseudomonal agents Sepsis/ septic shock but no risk features of MDR—One anti-pseudomonal agentrisk factors of MDR but no sepsis/ septic shock—one anti-pseudomonal agent No sepsis/ no risk factors of MDR—Broad spectrum antibiotic (no anti-pseudomonal coverage required) Duration—7 to 14 days
Nosocomial pneumonia [hospital acquired pneumonia (HAP) and ventilator associated pneumonia (VAP)]	*Acinetobacter baumannii, Klebsiella pneumoniae, Pseudomonas aeruginosa*	New or progressive infiltrates on a chest radiograph with fever>100.4° F; leucocytosis (>12,000/μl) or leucopenia (<4000/ μl); altered mental status; new onset purulent sputum or change in sputum character; worsening gas exchange	HAP: Expectorated sputum: Culture growth is to be considered significant if $\geq 10^5$ CFU/mL VAP: Endotracheal aspiration or mini bronchoalveolar lavage (BAL): Culture growth is considered to be significant if $\geq 10^5$ CFU/mL for tracheal aspirate and $\geq 10^3$ CFU/mL for BAL.	Risk factors of MDR or shock—2 anti-pseudomonal No risk factors of MDR or shock—1 anti-pseudomonal Duration—7 days
Complicated urinary tract infection (catheter associated UTI/ pyelonephritis)	*Escherichia coli, Klebsiella pneumoniae*	Fever, urinary symptoms (dysuria, burning micturition, supra-pubic pain, urinary frequency and urgency), flank pain/ costovertebral angle tenderness, features of sepsis	Urine routine—for pyuria Urine culture from mid—stream urine Blood culture in pyelonephritis Abdominal/pelvic imaging	Broad spectrum antimicrobial with ESBL coverage Duration—5–14 days

Table 21.3 Landmark studies on treatment options of MDR gram negative organisms (Paterson et al. 2004; Zanetti et al. 2003; Cheng et al. 2017; Lee et al. 2015; Harris et al. 2018; Paul et al. 2018)

S.n	Authors	Methodology	Outcome
1	Paterson et al. (2004)	Prospective observational study—ESBL producing *Klebsiella pneumoniae* ($n = 85$)—Carbapenem vs others	Carbapenem was associated with significantly lesser mortality
2.	Zanetti et al. (2003)	Randomized controlled trial ($n = 209$)—nosocomial pneumonia—ESBL producing *Klebsiella pneumoniae*—Imipenem vs Cefepime	Carbapenem was associated with significantly lesser mortality
3.	Cheng et al. (2017)	Case control study—Cefepime or meropenem ($n = 41$) vs piperacillin—tazobactam ($n = 41$) in blood stream infection due to AmpC producing *Enterobacter cloacae*	Piperacillin tazobactam not inferior to cefepime or carbapenem
4.	Lee et al. (2015)	Cefepime ($n = 72$) vs carbapenem ($n = 72$) in blood stream infection due to AmpC producing Enterobacteriaceae	Cefepime not inferior to or carbapenem
5.	Harris et al. (2018)	Randomized controlled trial ($n = 379$)—E.coli or *Klebsiella pneumoniae* resistant to ceftriaxone and susceptible to piperacillin tazobactam (PT)—PT vs meropenem	PT was not non-inferior to meropenem in 30-day mortality
6.	Paul et al. (2018)	Randomized controlled trial ($n = 406$)—carbapenem resistant organisms—colistin vs colistin plus meropenem	Combination not superior to monotherapy

in blood stream infections (D'Angelo et al. 2016), (Paul et al. 2018). For AmpC hyperproducers, carbapenems are the drug of choice but several studies have shown that cefepime has shown to be a good alternative to carbapenems, especially in low inoculum infections with lower MIC (D'Angelo et al. 2016). Combination therapy with two or more active drugs (when available), dosed optimally, is associated with increased efficacy in the treatment of carbapenem resistant infections. Studies have shown good results if one of the drugs used in combination is a carbapenem (Bassetti et al. 2017). Other drugs used in combinations are based on the susceptibility profile and include polymyxins, tigecycline, fosfomycin, etc. KPC producing organisms may be treated with newer antibiotics such as ceftazidime-avibactam and meropenem-vaborbactam (van Duin et al. 2018), (Lee and Baker 2018). However, NDM producing organisms require polymyxin B as a part of their therapy (Jean et al. 2015).

Since beta-lactams have time-dependent activity, extended infusion over 3–4 hours has been advocated to increase the time above minimum inhibitory concentration with the same total dosage. Several studies have shown that such a strategy is associated with better outcomes (Yu et al. 2018), (Rizk et al. 2017). Inhalation of antibiotics like colistin or aminoglycosides as an adjunct in treatment of patients with lower respiratory tract infections has shown to be useful (Vardakas et al. 2018). Similarly, local instillation of antibiotics like intra-thecal colistin in gram negative meningitis or gentamicin containing bone cement following debridement in osteomyelitis has shown to have some benefit (Bargiacchi and De Rosa 2016).

Table 21.4 Newer antimicrobials and their coverage (Katsube et al. 2017; Scott 2016; Sader et al. 2018; Zhanel et al. 2018; Shaeer et al. 2019; Zhanel et al. 2016)

Newer antimicrobials	ESBL	KPC	NDM	OXA48	*MDR Pae*	*MDR Aba*
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes
Ceftolozane-Tazobactam (CWSI)	Yes				Yes	Yes
Ceftazidime-Avibactam (CWSI)	Yes	Yes		Yes	Yes	
Aztreonam-Avibactam (CWSI)	Yes	Yes	Yes	Yes	Yes	
Imipenem-Relebactam (CWSI)	Yes	Yes				
Meropenem-Vaborbactam (CWSI)	Yes	Yes				
Plazomicin (aminoglycoside)	Yes	Yes		Yes	Yes	
Eravacycline (Fluorocycline)	Yes	Yes	Yes	Yes		Yes

CWSI Cell Wall Synthesis inhibitor

21.4 Newer Antibiotics and Treatment Strategies

In the last few years, a handful of new antibiotics have been developed to tackle the growing menace of resistant gram negative organisms due to low interest of the pharmaceutical industry. The newer antibiotics have been summarized in Table 21.4 based on their coverage of the key resistant gram negative organisms.

Preliminary research has shown that novel classes like teixobactin have good gram negative activity as well (Iyer et al. 2019). Several alternatives to antibiotics are being tried in recent times—bacteriophage, antimicrobial peptides, toll like receptors, monoclonal antibodies, antibiotic hybrids, and nanoparticles (Rello et al. 2019).

21.5 Conclusion

Infections with gram negative organism are becoming increasingly difficult to manage. Early diagnosis and rapid initiation of correct antimicrobials for the correct duration is the need of the hour. There is a need for further research in the development of newer drugs/strategies for treatment. These treatment strategies have to be coupled with effective antimicrobial stewardship and infection control practices to curb the development of further resistance.

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Management of MRSA, VRE

22

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22.1 Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) was described by Barber M in 1961, soon after its introduction in October 1960 (Barber 1961), and outbreaks of MRSA were reported in the early 1960s (Benner and Kayser 1968). Methicillin resistance in *S. aureus* is defined as an oxacillin minimum inhibitory concentration (MIC) of ≥4 mcg/mL (National Committee for Clinical Laboratory Standards 2013). Since that time, MRSA has spread worldwide, and the prevalence of MRSA has increased in both health care and community settings.

22.2 Prevalence

The prevalence of MRSA isolates in intensive care units in the USA is 60 percent (National Nosocomial Infections Surveillance System 2004), and more than 90,000 invasive infections due to MRSA occurred in the USA in 2005 (Klevens et al. 2007). The incidence of MRSA varies from 25% in western part of India (Patel et al. 2010) to 50% in South India (Gopalakrishnan and Sureshkumar 2010). Community acquired MRSA has been increasingly reported from India (D'Souza et al. 2010). The overall prevalence of methicillin resistance was found to be 41% in a study conducted in 15 tertiary care centers in India (Joshi et al. 2013).

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22.3 Mechanism of Resistance

Methicillin resistance is mediated by PBP-2a, a penicillin-binding protein encoded by the *mecA* gene that permits the organism to grow and divide in the presence of methicillin and other beta-lactam antibiotics. The *mecA* gene is located on a mobile genetic element called staphylococcal chromosome cassette (SCC*mec*). A single clone probably accounted for most MRSA isolates recovered during the 1960s; by 2004, six major MRSA clones emerged worldwide, labeled as SCC*mec* I to VI (Kreiswirth et al. 1993; Crisóstomo et al. 2001; Enright et al. 2002; Ito et al. 2004; Oliveira et al. 2001). Dissemination of resistance was mediated by horizontal transfer of the *mecA* gene and related regulatory sequences (Archer et al. 1994).

22.4 Health Care-Associated MRSA

HA-MRSA is defined as MRSA infection that occurs >48 h following hospitalization (hospital-onset, HA-MRSA, formerly "nosocomial") or MRSA infection that occurs outside of the hospital within 12 months of exposure to health care (e.g., history of surgery, hospitalization, dialysis, or residence in a long-term care facility; community-onset, HA-MRSA) (Klevens et al. 2007). HA-MRSA is associated with severe, invasive disease, including skin and soft tissue infection, bloodstream infection (BSI), and pneumonia (Klevens et al. 2007; Wisplinghoff et al. 2004; Boyce 1992; Klevens et al. 2006; Cosgrove et al. 2003). HA-MRSA strains tend to have multidrug resistance and carry staphylococcal cassette chromosome (SCC*mec*) type II (Naimi et al. 2003). Worldwide, HA-MRSA prevalence varies considerably, from <1% in Scandinavia to up to 40% in Japan, Israel, and elsewhere in Europe (Sader et al. 2006; Voss et al. 1994)

22.5 Community Acquired MRSA (CA-MRSA)

CA-MRSA is defined as MRSA infection that occurs in the absence of health care exposure (Klevens et al. 2007). CA-MRSA is most often associated with skin and soft tissue infections in young, otherwise healthy individuals (Fridkin et al. 2005). Most CA-MRSA strains are sensitive to non-beta-lactam antibiotics, although a multidrug-resistant isolate has been described among men who have sex with men (Diep et al. 2008; Diep et al. 2006a). This strain contains the pUSA03 plasmid and carries resistance genes for beta-lactams, fluoroquinolones, tetracycline, macrolides, clindamycin, and mupirocin (Diep et al. 2006a). Most CA-MRSA strains frequently carry SCC*mec* type IV or V and frequently carry genes for the cytotoxin Panton–Valentine leukocidin that confers enhanced virulence (Diep et al. 2006a; Baba et al. 2002; Diep et al. 2006b; Ma et al. 2002; Tenover et al. 2006; King et al. 2006)

22.6 Risk Factors

The increase in MRSA prevalence in hospital and community settings has been attributed to multiple factors. Risk factors for health care-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) are described below (Table 22.1). More important risk factors will be discussed here.

Antibiotic use—MRSA probably arose due to antibiotic selective pressure (Barber 1961; Diep et al. 2008). In a study, antibiotic prescriptions demonstrated a powerful positive association with MRSA bloodstream infection rates, which was largely attributable to lincosamides (Coeff: 0.257, 95% CI: 0.177, 0.336, $P < 0.001$), glycopeptides (Coeff: 0.223, 95% CI: 0.175, 0.272, $P < 0.001$), and sulfonamides (Coeff: 0.166, 95% CI: 0.082, 0.249, $P < 0.001$) (Andreatos et al. 2018). In another study done in Turkey, use of antibiotics [ampicillin-sulbactam and/or amoxicillin-clavulanate, fluoroquinolones, aminoglycosides, piperacillin-tazobactam (TZP), meropenem (MEM), imipenem (IPM), vancomycin (VAN), cephalosporins and teicoplanin (TEC)] was found to be statistically significantly higher in the case group by univariate analysis. In multivariate analysis, it was determined that TZP (OR = 6.82; $p < 0.001$), IPM (OR = 3.97; $p = 0.023$), and VAN (OR = 8.46; $p = 0.001$) use were independent risk factors in MRSA bacteremia (Atmaca et al. 2014).

Cephalosporins were implicated in a case-control study of 387 patients with S. aureus infection (half with MRSA and half with methicillin-susceptible S. aureus [MSSA]); patients who had received cephalosporins for ≥5 days were three times more likely to acquire MRSA than those who had not received cephalosporins (Hill et al. 1998; Asensio et al. 1996).

HIV infection—In a recently published meta-analysis involving 9772 patient records, 69 were included, comprising 30,050 HIV+ patients from 21 countries. Authors estimated the pooled worldwide prevalence of MRSA in people living with HIV to be 7% (95% CI 5–9%, 1623/30,050), with the highest prevalence in Southeast Asia (16%, 95% CI 9–24%) and the region of the Americas (10%; 95% CI 7–13%) and lowest prevalence in the European region (1%; 95% CI 0–1%). Globally, we estimated approximately 2,659,000 (95% CI 1,835,000–3,303,000) HIV+ patients with colonized MRSA. Potential risk factors for MRSA colonization in HIV+ patients included previous MRSA infection (OR, 7.5; 95% CI, 3.91–14.37),

Table 22.1 Risk Factors for HA- MRSA and CA-MRSA

HA-MRSA	CA-MRSA
Recent hospitalization	HIV infection
Recent surgery	Infection drug use
Residence in long-term care facility	Prior antibiotic use
Hemodialysis	Incarceration
Indwelling catheters	Military services
	Sharing needles, razors, and other sharp objects
	Men who have sex with men
	Sharing sports equipment

hospitalization in the past year (OR, 1.87; 95% CI 1.11–3.16), and use of antibiotics (OR, 2.52; 95% CI 1.39–4.58). Risk factors included advanced immunosuppression (CD4 count <50 cells/μL), high plasma HIV RNA (>100,000 copies/μL), and lack of antiretroviral therapy.

22.7 Injection Drug Use

In one report summarizing data from six Emerging Infections Program sites in the USA between 2005 and 2016; injection drug users were 16 times more likely to develop an invasive MRSA infection than noninjection users; infections included bacteremia, endocarditis, and osteomyelitis (Jackson et al. 2018). The proportion of invasive MRSA cases that occurred among injection drug users increased from 4 to 9

22.8 Presence of an Indwelling Hemodialysis Catheter

National surveillance report for England indicated that the relative risk of MRSA bacteremia was approximately 100-fold higher for dialysis patients than for the general population and was eightfold higher for patients using a catheter than for those with an arteriovenous fistula (Fluck et al. 2009). In addition, another surveillance report from the USA also indicated that dialysis patients had a 100-fold higher risk of MRSA infection than the general population (Centers for Disease Control and Prevention (CDC) 2007). Residence in a long-term care facility. However, in a single-center report from Brazil in 2010–2013, 38.5% of *S. aureus* was MRSA (Fram et al. 2015), whereas the methicillin resistance percentage was 31.0% in surveillance data from Brazil in 2005–2008(Gales et al. 2009).

22.9 Transmission

Health care-associated MRSA (HA-MRSA) strains are most commonly transmitted to patients via the transiently contaminated hands of health care workers. Hospitalized patients may also acquire HA-MRSA from contaminated environmental surfaces. Community-associated MRSA (CA-MRSA) strains are most commonly transmitted by direct contact with a colonized or infected individual.

22.10 Colonization

Individuals colonized with MRSA serve as a reservoir for transmission. MRSA can colonize the skin and nares of hospitalized patients, health care workers, and healthy individual. In a study involving 508 patients, with an average follow-up time of 28.5 days, prevalence of MRSA was found to be 8.9% (Heinze et al. 2019). Colonization increases the risk for MRSA infection (National Nosocomial Infections Surveillance System 2004). Colonization can occur by contaminated wounds or

dressings of infected patients, contact with another individual's colonized intact skin, contact with contaminated inanimate objects or by inhalation of aerosolized droplets from chronic nasal carriers.

22.11 Environmental Contamination

MRSA-contaminated surfaces can serve as reservoirs for MRSA transmission (Nkuwi et al. 2018).

In a study done in Tanzania, a total of 200 environmental samples from high touch items were processed and out of these MRSA was 19.5% with significantly higher contamination in general wards. Patients' beds surfaces were the most contaminated among studied items (43.7%), while the surgical trolleys were least contaminated (7.7%). Presence of 10 or more patients in a room was an important significant correlate for methicillin-resistant S. aureus contamination by bivariate logistic regression model (odds ratio: 4.75, 95% confidence interval 1.624–13.895, $p = 0.004$) (Nkuwi et al. 2018). Similarly, 11.8% of surfaces were positive for MRSA in another study from Southern Ontario (Faires et al. 2012).

22.12 Prevention and Control

Prevention and control of MRSA infection are among the most important challenges of infection prevention. Factors in transmission include colonization, impaired host defences, and contact with skin or contaminated fomites

22.13 In Health Care Settings

22.13.1 Basic Infection Prevention Principles

Principles of infection prevention for reducing spread of MRSA include attention to careful hand hygiene and adherence to contact precautions for care of patients with known MRSA infection (Liu et al. 2011).

22.13.2 Hand Hygiene

Hand hygiene consists of cleaning hands with soap and water or an alcohol-based hand gel before and after clinical encounters with patients who have MRSA infection. The hand-hygiene promotion programme was started on May 2004 at the University Hospital of Liège after a baseline survey of compliance. During the campaign, it was noticed that the consumption of alcohol-based handrub solution and soap increased by 56% and 24%, respectively, and MRSA transmission rates decreased from 11,04 to 7,07 cases per 1000 admissions (Christiaens et al. 2006).

22.13.3 Contact Precautions

Contact precautions include use of gowns and gloves during clinical encounters with patients who have MRSA infection; multiple studies have demonstrated the efficacy of contact precautions for reducing spread of MRSA (Muto et al. 2003; Musuuza et al. 2019). In the setting of care for patients with active pulmonary infection due to MRSA (e.g., during aerosol-generating procedures such as intubation), masks may offer some benefit for reducing colonization among health care workers (Muto et al. 2003). Patients colonized or infected with MRSA may be cohorted with other such patients.

22.13.4 Active Surveillance

Active surveillance consists of performing screening cultures (of the nares, oropharynx, and/or perineum) to identify asymptomatic patients who are colonized with antibiotic resistant bacteria, with the goal of intervening to minimize the likelihood of spread to other patients (Muto et al. 2003) Different microbiological methods exist for surveillance testing; these include standard microbiology methods, selective media, and polymerase-chain reaction-based tests. Rapid whole-genome sequencing is an alternative method that may be useful for outbreak investigation but is not yet widely available.

The optimal role for active surveillance is not known, and there is insufficient evidence for a single routine approach (National Committee for Clinical Laboratory Standards 2013).

22.14 Decolonization

22.14.1 Routine Chlorhexidine Bathing

In a meta-analysis which included 26 studies with 861,546 patient-days and 5259 Hospital Acquired Blood Stream Infections (HABSIs) found that patient bathing with chlorhexidine significantly reduced the incidence of HABSIs in both ICU and non-ICU settings (Musuuza et al. 2019). However, the strength of evidence for non-ICU use was lower. As a horizontal infection prevention strategy that covers a broad spectrum of pathogens, chlorhexidine bathing is an effective, relatively low-cost intervention that should be implemented with high fidelity to achieve maximum impact.

22.14.2 Targeted Decolonization

Nasal decolonization with mupirocin ointment (2%) applied to nares twice daily for 5–10 days. MRSA nasal colonization appears to precede infection, although asymptomatic nasal carriage is not always identifiable in the setting of MRSA infections. In addition, the durability of MRSA decolonization is limited.

22.14.3 Environmental Cleaning

Meticulous cleaning of patient care surfaces is essential for control of MRSA environmental contamination. MRSA is sensitive to routinely used hospital disinfectants but can survive on surfaces for hours, days, or months. Its viability depends on a variety of factors including temperature, humidity, the number of organisms present, and the type of surface. Medical equipment should be dedicated to a single patient when possible to avoid transfer of pathogens via fomites. Equipment that must be shared should be cleaned and disinfected before use for another patient. Environmental services personnel should be included as an integral part of the infection prevention team. Checklists for cleaning frequently touched patient care surfaces (such as bed controls, light switches, doorknobs, etc.) can be useful for reinforcing consistency. Ultraviolet markers may be useful for monitoring thoroughness of room cleaning.

22.14.4 Antibiotic Stewardship

Injudicious use of antibiotics must be used. Infection control measures alongside with removal of key antibiotic selection pressures during a national antibiotic stewardship intervention predicted large and sustained reductions in hospital-associated and community-associated MRSA (Lawes et al. 2015).

22.14.5 Clinical Approach

Clinical approach to treatment depends on site of infection and severity of symptoms. MRSA can lead to bacteremia, pneumonia or soft tissue infection along with other infections.

22.14.6 Approach to Bacteremia

The clinical approach to S. aureus bacteremia consists of careful history and physical examination, infectious disease consultation, and diagnostic evaluation including echocardiography and additional imaging as needed.

History and physical examination—A careful history and physical examination is essential. For circumstances in which the source of bacteremia is uncertain, patients should be questioned carefully regarding potential portals of entry including recent skin or soft tissue infection and presence of indwelling prosthetic devices (including intravascular catheters, orthopedic hardware, and cardiac devices). Patients should also be questioned regarding symptoms that may reflect metastatic infection.

The physical examination should include careful cardiac examination for signs of new regurgitant murmurs or heart failure. A vigorous search should be

undertaken for the clinical stigmata of endocarditis, including evidence of small and large emboli with special attention to the fundi, conjunctivae, skin, and digits. A neurologic evaluation should be undertaken for evidence of focal neurologic impairment; it is also important as a baseline examination should neurologic deficits develop later.

— Bedside infectious disease consultation is an important component of management for patients with S. aureus bacteremia and should occur whenever feasible.

Diagnostic evaluation—In general, blood cultures positive for S. aureus should be respected as a clinically significant finding that should prompt clinical evaluation and initiation of empiric therapy. All patients with S. aureus bacteremia should undergo echocardiography to evaluate for presence of endocarditis. Additional diagnostic imaging should be tailored to findings on history and physical examination.

22.14.7 Echocardiography

All patients with S. aureus bacteremia should undergo echocardiography to evaluate for presence of endocarditis (Cosgrove et al. 2003; Naimi et al. 2003). Transthoracic echocardiography (TTE) should be performed first (Naimi et al. 2003); identification of a vegetation on TTE usually obviates the need for transesophageal echocardiography (TEE), although TTE is not enough for ruling out infective endocarditis (IE) (Sader et al. 2006; Voss et al. 1994). The results of echocardiography are useful even when the study is negative, as the absence of IE may impact decisions about the duration of antimicrobial therapy.

22.14.8 Imaging

Imaging should be tailored to findings on history and physical examination. Patients with back pain should be evaluated for vertebral osteomyelitis and discitis. Positron emission tomography/computed tomography (PET/CT) is a promising modality for assessing for metastatic sites of infection; however, thus far, evidence is insufficient to recommend routine use of PET/CT.

22.14.9 Treatment

MRSA bacteremia should always be considered as clinically significant. Treatment of S. aureus bacteremia includes prompt source control (such as removal of implicated vascular catheters and/or surgical drainage of abscess if present) and antimicrobial therapy.

22.14.10 Empiric Treatment

The optimal approach to empiric therapy in the setting of S. aureus bacteremia prior to availability of culture and susceptibility data is uncertain. Empiric antimicrobial therapy with activity against MRSA. Empiric treatment for MRSA consists of vancomycin, daptomycin, teicoplanin or linezolid. Once susceptibility results are available, if the isolate is methicillin-susceptible S. aureus (MSSA), antibiotic treatment should be de-escalated to a beta-lactam agent. Table 22.2.

22.14.11 Combination Therapy

There is no role for routine use of combination therapy (such as vancomycin plus gentamicin or rifampin) for treatment of MRSA bacteremia; combination therapy may be useful in the presence of a prosthetic device or for salvage therapy (Ito et al. 2004). Vancomycin combined with gentamicin for treatment of MRSA bacteremia and native valve infective endocarditis has been associated with an increased risk of nephrotoxicity (Oliveira et al. 2001).

22.14.12 Alternative Agents

Tedizolid, Telavancin, TMP-SMX, Minocycline, Doxycycline, Ceftaroline or clindamycin may be used. HA-MRSA may be resistant to clindamycin and doxycycline.

Soft tissue infection.

Patients with skin and soft tissue infections known or suspected to be due to MRSA may present with cellulitis, abscess, or both. Patients with cellulitis should be managed with antibiotic therapy. Patients with abscess should undergo incision and drainage, and debrided material should be sent for culture and susceptibility testing.

Empiric coverage for MRSA is generally warranted for treatment of skin and soft tissue infections, given the high community prevalence of MRSA. Antibiotic therapy should be tailored to culture and susceptibility data when available. Patients with mild infection (localized involvement with no systemic symptoms) may be treated with oral antibiotic therapy.

Parenteral antibiotic therapy—Treatment with parenteral antibiotic therapy is warranted in the following circumstances:

● Extensive soft tissue involvement ● Signs of systemic toxicity ● Rapid progression of clinical manifestations ● Persistence or progression of symptoms after 48–72 h of oral therapy ● Immunocompromise proximity of soft tissue infection to an indwelling device (such as a prosthetic joint or a vascular graft); soft tissue infection should be considered a manifestation of device infection if it originates on the skin directly overlying the prosthesis site.

Table 22.2 Drugs used for MRSA infection

Drug	Group	Mechanism of action	Dose	Renal dose adjustment	Hepatic dose adjustment	Pregnancy category	Side effects	Special note
Vancomycin	Glycopeptide Bactericidal	Inhibits cell wall synthesis	LD25–30 mg/kg IV (especially in septic shock) 15–20 mg/kgof actual BW IV q8–12 h	Required	None	C	Red neck syndrome, DRESS, fever, thrombocytopenia, Neutropenia hearing lose, nephrotoxicity	Individual dose >1gm/kg should be infused over1.5–2 h Daily dose should be limited to 2gms/day Trough level target 15–20 mcg/mL
Daptomycin	Lipopeptide	Depolarization of the bacterial cell membrane	6 mg/kgTBW IV over 30 min q24 h	Required	None	B	myopathy, peripheral neuropathy, and eosinophilic pneumonia (Bonten et al. 1998; Snyder et al. 2008). Serial measurements of serum creatine kinase should be monitored at least weekly, and daptomycin should be discontinued in patients with symptomatic myopathy and creatine phosphokinase (CPK) ≥5 times the upper limit of normal (ULN) or in asymptomatic patients With CPK ≥10 times the ULN	Do not use for primary pneumonia as inactive ny pulmonary surfactant Non compatible with dextrose containing fluids

Teicoplanin	Glycopeptide Bacteriostatic	Inhibits cell wall synthesis	LD 6 mg/kg IV 12 h for 3doses, then MD of 6 mg/kg IV 12 h. Severe Infection higher doses have been used LD 12 mg/kg iv 12 h 3 doses the MD 12	Required	None	B	Hypersensitivity, fever, skin reaction marked thrombocytopenia, anemia and neutropenia Red neck syndrome and nephrotoxicity lesser than vancomycin	
Linezolid	Oxazolidinone Bacteriostatic	Inhibits initiation of protein synthesis at the 50S ribosome	600 mg/kg PO/ IV q12h	None	None	C	Thrombocytopenia, anemia, lactic acidosis, peripheral neuropathy, serotonin toxicity, and ocular toxicity Can reversibly inhibit monoamine oxidase	Enhanced efficacy against strains producing toxins such as Panton-valentine leukocidin, alpha-hemolysin, and toxic shock Syndrome toxin 1

LD Loading Dose, *MD* Maintenance dose, *h* Hours, *TBW* Total body weight, *ABW* Actual body weight

Antibiotics of choice—Parenteral agents of choice for treatment of skin and soft tissue infection when MRSA is known or suspected include vancomycin, daptomycin, teicoplanin or linezolid.

Alternative agents: Delafloxacin, Omadacycline, Ceftaroline (and ceftobiprole),

Tigecycline, and quinupristin-dalfopristin should not be used for treatment of skin and soft tissue infections due to MRSA.

22.14.13 Duration of Therapy

The duration of therapy for *S. aureus* bacteremia depends on the etiology of infection (Oliveira et al. 2001). Determination of treatment duration requires differentiation of patients with uncomplicated *S aureus* bacteremia (who may be cured with 14 days of intravenous therapy from the first negative blood culture) from patients with complicated *S. aureus* bacteremia *(*who require longer duration of intravenous treatment).

Patients with mild infection who warrant outpatient management with oral antibiotic therapy should have repeat evaluation after 24–48 h to verify that there is a clinical response (National Committee for Clinical Laboratory Standards 2013). Patients with MRSA responsive to oral therapy are typically treated for 5 days; extension of the duration (up to 14 days) may be warranted in the setting of severe infection and/or slow response to therapy. Lack of response may be due to infection with resistant organism(s), inadequate adherence, or presence of a deeper, more serious infection than previously realized.

Patients with infection warranting parenteral therapy (in the absence of bacteremia or involvement beyond soft tissue) are typically treated for a total duration of 5–14 days. Once there are signs of clinical improvement with no evidence of systemic toxicity, antibiotics may be transitioned from parenteral to oral therapy.

For intermediate vancomycin-resistant staph. Aureus (VISA) (vancomycin MIC 4–8 mcg/mL) vancomycin-resistant staph. Aureus (VRSA) (vancomycin MIC >8 mcg/mL) treatment options are linezolid, daptomycin (confirm susceptibility), TMP-SMX, minocycline, ceftaroline, quinupristin-dalfopristin.

22.14.14 Prognosis

Mortality rates of 20–40% have been reported in most case series of patients with *S. aureus* bacteremia; these rates have not changed over the past several decades. Mortality is higher among patients with underlying comorbidities, methicillin-resistant *S. aureus* (MRSA) infection and/or time to positivity of blood cultures $\leq$12 h.

22.15 VRE

22.15.1 Introduction

Vancomycin-resistant *Enterococcus* (VRE), belonging to the species *Enterococcus faecium*, was first encountered in clinical isolates in England and France in 1986, followed the next year by isolation of VRE *faecalis* in the USA (Leclercq et al. 1988; Uttley et al. 1988; Sahm et al. 1989). In Europe, the rise of VRE was principally in the community setting, due to transmission from animal food products to humans, thought to arise from the use of a glycopeptide antibiotic avoparcin as a growth promoter in livestock (Acar et al. 2000),whereas in the USA the predominance of VRE was in the hospital setting, believed to be due to the increasing use of the glycopeptide antibiotic vancomycin (Kirst et al. 1998), Subsequently, the USA experienced a rapid spread of VRE in hospitals in the 1990s, Europe followed suit in the 2000s, and eventually a worldwide spread ensued (Bonten et al. 2001; Frieden et al. 1993; The European Antimicrobial Resistance Surveillance System 2015). In 2002, the threat of VRE colonization and infections increased when the first patient case of VRE transmitting *vanA* resistance genes to methicillin-resistant *Staphylococcus aureus* (MRSA) to form a vancomycin-resistant *Staphylococcus aureus* (VRSA) isolate was reported (Chang et al. 2003). Currently, 54 different species and two subspecies of enterococci have been described, with *E. faecalis* and *E. faecium* being the most clinically relevant species, isolated in the US at a ratio of 1.6:1, respectively (The European Antimicrobial Resistance Surveillance System 2015). *E. faecalis* is more pathogenic than *E. faecium*, but the latter exhibits more resistance, composing the majority of VRE infections. The emergence of VRE as an important nosocomial pathogen is due to its propensity for colonization of the gastrointestinal (GI) tract, persistence in hospital environments, genome plasticity, mobile genetic elements, and increased mortality (Chang et al. 2003).

22.15.2 Mechanism of Resistance

Until the last few decades, enterococci could be treated with penicillin, ampicillin, or vancomycin with or without an aminoglycoside. Some enterococci have now acquired resistance to these and many other agents as a result of mutations.

One mechanism, involving pheromone-responsive plasmids, causes plasmid transfer between *Enterococcus faecalis* isolates at a very high frequency (Dunny et al. 1995).

- Another mechanism involves other plasmids that can transfer among a broad range of species and genera, although usually at a moderately low frequency (Murray 1990).
- A third mechanism (conjugative transposition) involves transfer of specialized transposons at low frequency but to a very broad range of different kinds of bacteria (Clewell and Gawron-Burke 1986). Conjugative transposons are relatively

nonselective in their host range and are one of the few types of elements known to have crossed the gram-positive/gram-negative barrier in naturally occurring clinical isolates and to then cause resistance in these various hosts (Roberts 1990).

- A fourth mechanism involves the transfer of large fragments of chromosomal DNA directly from one cell to the other via conjugation. This has been described with conjugative transposons and, in *E. faecalis,* with pheromone-responsive plasmids; with the latter, the transfer of chromosomal DNA appears to be dependent upon recombination occurring between homologous sequences present on these plasmids and the chromosome (Manson et al. 2010).

22.15.3 Colonization

VRE colonization is identified through the use of rectal or perirectal swab cultures or stool cultures. The overall sensitivity of rectal swab cultures for detection of VRE was 58% in one report but varied directly with VRE density in stool from 100% at high densities (≥7.5 logs per gram) to 0% at low densities (≤4.5 logs per gram) (Naimi et al. 2003). Both prior antibiotic exposure and skin colonization with VRE were more common in patients with high stool densities. The authors speculated that the high false-negative rate of rectal swab cultures may contribute to the increasing prevalence of VRE. The majority of VRE colonization occurs in the GI tract, but can also be found to a lesser extent on the skin, in the genitourinary (GU) tract, and in the oral cavity (Linden 2007; Cetinkaya et al. 2000) *E. faecalis* is the major colonizer in these sites. Once GI colonization with VRE occurs, it can persist for months to years and efforts at decolonization are typically transitory, with recurrence of VRE days or weeks later (Baden et al. 2002; Bonten et al. 1998). Health care workers' hands are the most consistent source of transmission (Snyder et al. 2008). VRE can persist for up to 60 min on hands and as long as 4 months on surfaces (Noskin et al. 1999; Kramer et al. 2006). The common pathway for nosocomial VRE starts with acquisition via person-to-person contact or exposure to contaminated objects. Gut microbiota are then suppressed through antimicrobial selective pressure, allowing for overgrowth of VRE, as it is intrinsically resistant to several antibiotics. When the patient becomes immunosuppressed, VRE can flourish, causing a clinical illness (Linden 2007).

Transmission After vancomycin-resistant enterococci (VRE) have been introduced into a healthcare setting, transmission is determined by selective pressure due to antimicrobial use, the proportion of colonized patients, the availability of susceptible patients, and adherence to prevention efforts. The risk increases significantly in an intensive care unit once the proportion of patients exceeds 50%.

22.15.4 Risk Factors

The most consistently observed risk factor for hospital acquisition of VRE is previous treatment with antimicrobials, particularly vancomycin and cephalosporins (Table 22.3). As an example, a prospective study of 126 adult intensive care units

Table 22.3 There are a number of risk factors for vancomycin-resistant enterococci (VRE) colonization and infection

Risk factors
Previous antimicrobial therapy
Patient characteristics
Colonization pressure
Exposure to contaminated surface
Residence to long care facility

(ICUs) in 60 hospitals found that vancomycin and cephalosporin use were significantly higher in patients with VRE, after controlling for the type of ICU and rates of VRE elsewhere in the institution (Diep et al. 2006a). In another report, colonization or infection was associated with a longer duration of therapy with ceftazidime (13.2 versus 4.6 days in noninfected controls (Voss et al. 1994)).

Use of multiple agents with a broad spectrum of activity may predispose patients to colonization with resistant enterococci, probably via alteration of the normal bowel flora.

(Baba et al. 2002). Among patients with VRE in stool, the administration of antibiotics active against anaerobic organisms can increase the density of stool colonization with VRE, which decreases after discontinuation of these agents (Fridkin et al. 2005).

Exposure to daptomycin, an antibiotic frequently used to treat VRE, can lead to VRE isolates with resistance to linezolid and daptomycin. In one study including more than 80 patients with daptomycin and linezolid non-susceptible VRE, risk factors included recent invasive surgical procedures and daptomycin exposure (Diep et al. 2006b).

Patient characteristics—A number of patient characteristics other than.

Antimicrobial therapy have been associated with a high risk of VRE colonization. These include hospitalization longer than 72 h, significant underlying medical conditions (end-stage renal disease requiring dialysis, cancer, transplant recipient), requirement for ICU, and invasive devices (Enright et al. 2002).

Colonization pressure—Colonization pressure is an important risk factor for acquisition of VRE (Cosgrove et al. 2003; Ma et al. 2002). Colonization pressure in hospitals can lead to substantial increases in VRE colonization. A review of 1039 patients admitted to a general medicine ward demonstrated that colonization with VRE increased from 3.8% on admission to 32% during hospitalization; 60% of the VRE isolates were the same strain (Tenover et al. 2006). Indeed, hospitalization is strongly correlated with risk of VRE colonization (Tenover et al. 2006; King et al. 2006). Colonization pressure may outweigh other risk factors including antibiotic use once 50% or more of patients within the unit are colonized with VRE.

Exposure to contaminated surfaces—Exposure to contaminated surfaces in patient rooms, even after routine discharge cleaning, may be associated with VRE acquisition (Andreatos et al. 2018; Atmaca et al. 2014). For example, several outbreaks caused by transmission of VRE from contaminated medical equipment have been reported. Implicated medical equipment included rectal thermometers, tympanic thermometers, and contaminated electrocardiogram leads (Voss et al. 1994; Hill et al. 1998; Asensio et al. 1996).

Transmission of VRE from environmental surfaces to the hands or gloves of healthcare workers has been well documented. Forty-six percent of healthcare workers who touched bedrails and bedside tables in rooms of colonized patients in

turn contaminated their gloves with VRE in one study (Sabbagh et al. 2019). Another study demonstrated that gloves or hands contaminated through contact with contaminated environmental surfaces can transfer VRE to approximately 10% of uncontaminated surfaces that are subsequently touched by other healthcare workers (Jackson et al. 2018). Patients with VRE colonization are associated with greater environmental contamination than patients with VRE infection (Fluck et al. 2009). Specific education of environmental services personnel leads to improved compliance with cleaning protocols and decreased environmental contamination with VRE (Centers for Disease Control and Prevention (CDC) 2007). A prospective quasi-experimental study showed that improved environmental cleaning significantly reduced the rate of VRE acquisition in a medical ICU (Fram et al. 2015). This study was divided into four phases: a baseline period, a period including education to improve cleaning practices, a "washout" period, and a period including a multimodal hand hygiene initiative. Patients were screened for VRE on admission to ICU and daily thereafter. Enhanced cleaning with a detergent-disinfectant was found to reduce environmental and hand contamination as well as VRE acquisition. Novel technologies such as steam vapor (Gales et al. 2009), UV-C irradiation (Heinze et al. 2019), vaporized hydrogen peroxide (Nkuwi et al. 2018), and copper-lined surfaces (Faires et al. 2012) may further decrease environmental contamination and transmission of VRE.

22.15.5 Residence in Long-Term Care Facilities—Residents of Long-Term Care Facilities

(LTCFs) appear to be a reservoir for VRE. In a prospective cohort study, 45% of patients admitted to an acute care hospital from an LTCF had rectal colonization with VRE; risk factors included prior use of antibiotics and the presence of a decubitus ulcer.

(Liu et al. 2011).

Around the world, the rates of VRE are at their highest in North America. According to the National Healthcare Safety Network (NHSN), from 2009 to 2010, 35.5% of enterococcal hospital-associated infections were resistant to vancomycin, ranking as the second most common cause of nosocomial infections in the USA (Sievert et al. 2013).

22.15.6 Infection Control

Prevention of infection with vancomycin-resistant enterococci (VRE), as with any multidrug-resistant organism, requires a multifaceted approach including general infection prevention (e.g., optimal management of vascular and urinary catheters), accurate and prompt diagnosis and treatment, prudent use of antimicrobial drugs, and prevention of transmission (Christiaens et al. 2006). Methods for prevention will be summarized here.

Several different strategies for the prevention, control, and eradication of VRE have been studied. These include hand hygiene, contact precautions, cohorting of colonized patients, decolonization, surveillance cultures, and source control.

Judicious use of antimicrobial drugs (called antimicrobial stewardship) is another modality, but its relative importance for control of VRE is unclear (Muto et al. 2003). Agents that would be targeted include vancomycin, third-generation cephalosporins, and anti-anaerobic drugs.

22.15.7 Clinical Approach

Enterococcus infection may lead to bacteremia, infective endocarditis, skin and soft tissue infection, intra-abdominal and pelvic infection, urinary tract infection, and central nervous system infection. Optimal approach for treatment of enterococcal infection due to vancomycin-resistant *E. faecium* is uncertain. Infective disease specialist consultation is required because of this. One agent, linezolid, is US Food and Drug Administration (FDA) approved for treatment of infections caused by vancomycin-resistant enterococci (VRE; prior approval of quinupristin-dalfopristin has been removed). The utility of this agent for treatment of endocarditis is uncertain, although there are anecdotal cases suggesting some utility. The resistance profile of vancomycin-resistant enterococci isolates should be evaluated carefully in conjunction with infectious diseases expertise when selecting appropriate therapy for such organisms. The approach to treatment of such isolates should be assessed in each individual case. Vancomycin-resistant *E. faecium* isolates often have concurrent high-level resistance to beta-lactams and aminoglycosides. In contrast, vancomycin-resistant *E. faecalis* are usually susceptible to beta-lactams, as are *E. gallinarum* and *E. casseliflavus* (which are intrinsically vancomycin resistant). The newer agents linezolid, daptomycin, and tigecycline have activity against both vancomycin-resistant *E. faecalis* and *E. faecium*, whereas quinupristin-dalfopristin has activity against *E. faecium* but not *E. faecalis*.

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Fungal Infections in the ICU

23

Ian Molyneaux and Somnath Bose

A 35-year-old male patient with a history of kidney transplantation is admitted to the intensive care unit after a Graham patch procedure for treatment of a gastric perforation. He is in septic shock and is being treated with Vancomycin and Piperacillin with Tazobactam and his hemodynamics are being supported with Norepinephrine and Vasopressin. He shows no hemodynamic improvement over 48 h despite resolution of his surgical issues and no new identifiable sources of infection.

What are his risk factors for fungal septicemia?
How would you choose antifungal therapy for this patient?
When should you initiate antifungal therapy?
What tests could you use to help with diagnosis of an invasive fungal infection?
How does his mortality change with an invasive fungal infection?

23.1 Pertinent Fungal Microbiology

Before delving into approaches for treatment of fungal diseases in the intensive care unit (ICU), a review of basic concepts of fungal microbiology and disease mechanisms will be briefly discussed.

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Fungi are eukaryotic organisms with the typical cellular features of those entities with some notable structural components. Fungal cells have a nuclear apparatus (nucleus with chromosomal material, nucleolus, nuclear membrane), a cytoplasm with cellular organelles (Golgi apparatus, mitochondria, etc.), and importantly a rigid cell wall external to their cellular membrane.

Although fungal cells are eukaryotes, they differ from mammalians cells in having a cell wall made from acetylglucosamine polymers known as chitin, polysaccharides, mucopolysaccharides, and glucans. (Bowman and Free 2006) The sterol component of the cytoplasm and cell membrane in fungal cells is primarily ergosterol as opposed to cholesterol in human cells. (Rodrigues 2018)

Fungi that are pathogenic can be divided into 4 different groups (Tan and Yang 2018)

1. Molds—e.g., Aspergillus. These pathogens grow as long branching filaments known as hyphae. These hyphae then form an intertwined network known as a mycelium. These characteristic features help with their identification.
2. True Yeasts—e.g., Cryptococci. They are unicellular and have a round or ovoid shape.
3. Yeast-Like Fungi—e.g., Candida. They are also unicellular with the same round or ovoid shape like true yeasts but can also form filaments known as pseudohyphae.
4. Dimorphic Fungi—e.g., Histoplasma. They will grow as yeasts when they are pathogens or at 37 degrees Celsius but in the environment or at 22 degrees Celsius, they will grow as mycelia.

23.2 Fungal Disease Mechanisms

Fungi are ubiquitous in nature and unlike bacteria and viruses, they are not known to derive any benefits from infecting humans (Kobayashi 1996). Some fungi, such as Candida, are normal commensal organisms to humans. In fact, lifelong colonization of the oral cavity, mucosal surfaces, and upper gastrointestinal tract with Candida occurs after a newborn is exposed to the fungus during birth while passing through the vaginal canal (Kobayashi 1996). Fungi that cause disease can also enter the human body through inhalation, e.g., Aspergillus and Histoplasma, iatrogenically, e.g., with indwelling catheters and lines or through trauma.

It is extremely rare for fungi to cause disease in immunocompetent patients. (Segal 2009) In fact, invasive fungal disease is a sign of a severely debilitated patient, such as critically ill ICU patients, or a bypass of normal immune defenses, such as with direct inoculation via colonized indwelling lines or catheters.

Normal epithelial and mucosal barriers are significant deterrents to fungal infections and are considered a major first line of defense (Weindl et al. 2010). If there is colonization with fungi on these surfaces, change in the normal host microbiological flora, such as with prolonged antibiotic use, or abnormal mucosal surfaces, as in with patients on chemotherapy, then fungal invasion can occur. As previously mentioned, it is also possible for fungi to circumvent this first line of defense by gaining direct host entry via invasive catheters and devices.

Once fungi bypass the host's barrier defenses they will normally encounter the innate immune response. Macrophages, Monocytes, and Dendritic Cells will recognize various fungal proteins and receptors as antigenic. Chitin and glucans of the fungal cell wall, for example, are known to stimulate the immune system (Templeton et al. 2018). This leads to a cascade of immune responses including cytokine release, antigen presentation, oxidative pathogen destruction, and proliferation of T-helper Cells and immunoglobulins (Charles Molnar 2012). All these processes are expected to lead to fungal cell destruction.

As demonstrated from the brief review of medical fungal microbiology above, many patients in the ICU are at risk for developing serious fungal infections. We further review the strategies of diagnosing and treating invasive fungal diseases and review the clinical manifestations of fungal disease pertinent to the intensivists.

23.3 Definition

Invasive Fungal Infection (IFI) is the term used to describe systemic, generalized, life-threatening, visceral, or deep-seated disease caused by pathogenic yeasts or molds (Hof 2010). Treatment in an ICU and the expertise of an intensivist and infectious disease specialist is sometimes required for these infections.

23.4 Epidemiology

23.4.1 Risk Factors for IFIs

There are many scoring systems that have been devised with the hopes of predicting patients who should be on either prophylactic or empiric treatment with antifungals. To date, none of these systems has been validated with any multi-center or randomized controlled clinical trials. Risk factors for IFIs are, however, well known and careful clinical assessment helps to guide initiation of antifungal therapy (Muskett et al. 2011).

High Suspicion for IFIs should be considered in patients who have any other following risk factors:

1. Candida Colonization.
2. Intra-Abdominal Infections or Gastrointestinal Perforations or Leaks, with higher risk in patients who have upper gastrointestinal pathology.
3. Indwelling Invasive Lines or Catheters (e.g., Central Lines).
4. Total Parenteral Nutrition.
5. Broad Spectrum Antibiotic Therapy.
6. High Severity of Illness (High APACHE II Scores).
7. Immunocompromised states including:

(a) Burn patients.
(b) Chemotherapy patients.
(c) Corticosteroid therapy.
(d) Transplant recipients of any kind.
(e) Neutropenia.
(f) Neonates.
(g) HIV/AIDS.

IFIs should also be considered in patients who also have the following risk factors (Ostrosky-Zeichner and Al-Obaidi 2009):

1. Hemodialysis.
2. Prolonged ICU stay.
3. Prolonged Mechanical Ventilation.
4. Diabetes Mellitus.
5. Major Surgery.

23.5 Types of Fungi Causing IFIS

Candida species account for more than 50% of invasive fungal diseases seen the ICU. (Yapar 2014) This is reflective of its role as a commensal organism in humans. Candida albicans remains the most common fungal species isolated with IFIs but non-albicans species are nowadays becoming increasingly common in ICUs.

Aspergillus spp. is the most common mold infection in the critically ill (Beed et al. 2014), usually causing pulmonary or sinus disease.

Cryptococcal infections remain a problem for individuals who are chronically immunosuppressed, e.g., patients with AIDS.

Histoplasma infections are only symptomatic in the immunocompromised, or in patients exposed to a very high inoculum. Patients will usually have the pre-requisite history of living in or travelling to endemic areas in the Midwestern or Southeastern United States, Central America, or Eastern Canada along with a large inoculum exposure history with, e.g., birds, bats, caves, or construction sites (Knox and Hage 2010).

All IFIs are known to have a high mortality rate often in excess of 30%, with mold infections exceeding the mortality rates of yeast infections (Zaragoza et al. 2008). Therefore early diagnosis and treatment are tantamount to favorable patient outcomes.

23.6 Clinical Presentation of Invasive Fungal Diseases

Candida infections cause the majority of IFIs followed by mold infections with Aspergillus (Yapar 2014).

Candida is known to create a biofilm that protects the organism from penetration by host immune defense mechanisms as well as by antifungal medications (Nobile and Johnson 2015). This feature along with its known commensalism helps to account for candida being the most prevalent fungal infection in the ICU.

23.6.1 Candida Infections

Invasive Candida Infections sometimes give only mild symptoms, such as fever or prodromal symptoms. They can also present with a full blown picture of septic shock. Visceral candida abscesses can present as any number of organ specific issues, ranging from pain, elevated organ specific serum biomarkers, e.g., elevated AST and ALT in liver abscesses, or organ dysfunction.

Clinical features that may hint to candida disease include eye lesions such as chorioretinitis and vitritis, skin lesions, which may be nodular or pustular and uncommonly muscle abscesses.

23.6.2 Aspergillus Infections

This fungus typically causes upper and/or lower respiratory issues after inhalation of conidia.

Sinus disease will present with nasal congestion, fever, facial, periorbital, or eye pain. In fact, sinus disease in the immunocompromised should prompt the clinician to consider a diagnosis of invasive fungal disease (Badiee and Hashemizadeh 2014).

Pulmonary symptoms will range from fever and cough to dyspnea and chest pain.

23.7 Diagnosis of IFIs

Isolation of fungal pathogens grown from blood or tissue cultures remain the gold standard for diagnosing invasive fungal disease.

The diagnosis of fungal infections in the ICU can be difficult due to several reasons (Ostrosky-Zeichner and Al-Obaidi 2009).

1. Blood cultures are only *positive in 50% of patients* who have invasive fungal infections and rarely isolate Aspergillus spp. or other mold pathogens.
2. Blood cultures may take up to 5 days to isolate a fungal pathogen.
3. Visceral Infections that are cultured or biopsied also may take several days before a result is obtained.
4. Non-sterile culture sites may make it difficult to differentiate between colonization and actual infection.
5. Pathognomonic radiology signs are not always present in ICU patients who have a dysfunctional immune system and these signs are not specific to particular fungal pathogens.

23.7.1 Common Molecular Diagnostic Methods

23.7.1.1 Beta-D-Glucan Assay

There are currently 5 commercially available assays available for this test. Fungitell, Endosafe-PTS, Fungitec-G, Beta-Glucan Test, and BGSTAR β-Glucan Test. (Wright et al. 2011)

These rapid diagnostic tests identify the Beta-D-glucan component of the fungal cell wall in blood and body fluids. Commercial tests measure activation of the coagulation cascade using horseshoe crab components. It is quoted as having a sensitivity of 57–81% and a specificity of 56–92%. This test, however, is potentially plagued with false positive results for ICU patients. Gram-positive bacterial infections are known to give false positives along with antibiotic therapy, such as with Amoxicillin with Clavulanic Acid. Dialysis membranes with cellulose material may also give false positive results.

The assay also does not differentiate between fungal species and cannot detect Cryptococcus.

Recommendations currently for this test is for use in conjunction with biopsy results and/or blood cultures. Of note, a negative beta-D-glucan assay is associated with a good negative predictive value for ruling out invasive fungal infection. In conjunction with an overall clinical picture, this assay could be helpful in deciding to stop unnecessary prescription of systemic antifungals (Theel and Doern 2013).

23.7.1.2 Galactomannan Assay

This is an immunoenzymatic process that detects the glactomannan fungal cell wall constituents in a patient's body fluid. This test is considered specific for Invasive Aspergillus disease and has been reported to have the highest sensitivity when performed on bronchoalveolar lavage specimens. Its highest sensitivity has been reported in patients who have received stem cell transplants or have hematological malignancies (Arvanitis et al. 2014). Accurate interpretation of the test is therefore more difficult in other critically ill patients. False positives have been reported in patients who have received beta-lactam antibiotics specifically Piperacillin Tazobactam or Plasmalyte infusions and the sensitivity of the test decreases with prior antifungal use.

23.7.1.3 Pharmacology of Antifungals

There are currently four different classes of medications that are used to treat IFIs

1. Azoles
2. Echinocandins
3. Polyenes
4. Antimetabolites

23.7.1.4 Azoles

Drugs in this class include

1. Fluconazole
2. Itraconazole

3. Voriconazole
4. Posaconazole
5. Isavuconazole

The primary mechanism of action of drugs in this class is the inhibition of lanosterol 14-alpha-demethylase. This enzyme is required for the synthesis of ergosterol which is the main component of fungal cell membranes. Without ergosterol to sustain a properly functioning cell membrane, fungal cells experience increased permeability and cell lysis. Despite this mechanism of action, the azoles are considered fungistatic for Candida species.

23.7.1.5 Echinocandins

Drugs in this class include

1. Micafungin
2. Caspofungin
3. Anidulafungin

The mechanism of action of drugs in this class is the inhibition the fungal enzyme Beta-1,3-d-glucan synthase. This enzyme is required for the normal synthesis of the glucan polymer components of the fungal cell wall. With loss of normal formation of glucans in the cell wall, the fungal cell is exposed to osmotic forces that lead to cell lysis. The Echinocandins are fungicidal to most Candida species and fungistatic to Aspergillus species (Lepak and Andes 2011).

23.7.1.6 Polyenes

Drugs in this class include Amphotericin B and nystatin. Amphotericin B is the main drug in this class that can be used to treat systemic disease. Its mechanism of action relates to its ability to bind to ergosterol, which as previously mentioned is an integral component of fungal cell membranes. Pores in the fungal cell wall develop, leading to leaking of fungal cellular material and fungal cell death. Amphotericin B has a broad spectrum of fungicidal activity against many types of fungal pathogens but its toxicity limits its use to severe invasive fungal diseases.

23.7.2 Antimetabolites

The main drug in this class used is Flucytosine which is also known as 5-fluorocytosine or 5-FC. Its mechanism of action is prevention of fungal protein transcription leading fungal cell death by fungal conversion of the 5-FC to 5-fluorouracil (5-FU). This inhibits fungal RNA and DNA synthesis. Monotherapy with 5-FC is limited because of the frequent development of resistance. Combination therapy of 5-FC with amphotericin B is recommended for the initial management of severe cryptococcal pneumonia and meningoencephalitis.

23.7.3 Management of IFIs

There are several proposed strategies to treat fungal infections in the ICU. Preventative antifungal treatment involves prophylactic administration of an antifungal in patients who have risk factors for fungal infection. Empiric antifungal treatment involves waiting until a patient develops signs and symptoms of an infection before starting antifungal therapy. Empiric treatment is associated with higher mortality in susceptible patients and prophylactic therapy is not associated with any mortality benefit and is associated with increased rates of antifungal resistance in non-neutropenic critically ill patients (Pappas et al. 2016).

Pre-emptive therapy involves starting antifungal therapy right when symptoms of an infection start or right before they start with the aid of screening tests such as Fungitell. Pre-emptive treatment may lead to improved survival but the problems of interpreting non-culture based diagnostic tests exist and also selecting the patients who should be screened remains a challenge (Feldman 2007).

Although many treatment algorithms and sophisticated scoring systems are used to determine whether or not antifungal therapy should be started in the critically ill patient with sepsis but there is no uniform consensus. There remains no substitute for good clinical judgment and individualized care (Ahmed et al. 2017)

The Infectious Disease Society of America (ISDA) has several recommendations and guidelines on the management of IFIs with the caveat that some of their recommendations are based on current expert consensus and variable qualities of evidence. These recommendations will likely be updated in the future when more trials or clinical studies are completed.

Early involvement of an infectious disease specialist in patients who are suspected to have an IFI is highly recommended.

23.8 Non-neutropenic Patients with Candida IFIs

Patients who have risk factors for IFIs where pre-emptive or empiric therapy is needed, the initial treatment should be with an Echinocandin such as Micafungin (Pappas et al. 2016).

An azole, such as fluconazole, can be considered in patients who have low risk factors for azole resistant pathogens.

23.9 Neutropenic Patients with Candida IFIs

Patients should initially be treated with an Echinocandin, such as Micafungin. An azole such as fluconazole can be used but only for patients who are not critically ill and have no risk factors for azole resistant organisms and have not been previously on azole therapy (Pappas et al. 2016).

23.10 Invasive Aspergillosis

Current recommendations are to treat invasive aspergillosis with Voriconazole. Initial combination therapy with Voriconazole and an Echinocandin or amphotericin B can be considered but currently there is not enough data to support a consensus on this approach as standard of care. Combination therapy can be used in patients who fail to respond to initial Voriconazole therapy.

Isavuconazole or amphotericin B can be used in place of Voriconazole (Patterson et al. 2016).

23.11 Cryptococcal Central Nervous System Infections

Current recommendations are to use Amphotericin B in combination with flucytosine (Perfect et al. 2010).

23.12 Pulmonary Histoplasmosis

Itraconazole has high activity against Histoplasma capsulatum and is recommended as first line therapy in mild, mild to moderate or localized infections. Moderate to severe infections should be treated with amphotericin B (Wheat et al. 2007; Dismukes et al. 1992).

Echinocandins have not been shown to be effective in vitro *against histoplasma species.*

*Any patient with an invasive fungal infection who has an invasive line or device that is suspected to the source of infection should have that line or device removed once it is safe and clinically feasible to do so. (*Patterson et al. 2016*).*

For most IFIs the minimum duration of therapy should be at least 14 days or until there is no further clinical evidence of ongoing infection. The duration of therapy should be decided in conjunction with an infectious disease specialist (Patterson et al. 2016).

23.12.1 Fungal Susceptibility Patterns

Candida Albicans—Resistance to antifungal therapy for the Albicans spp. remains low and thus therapy with an azole such as fluconazole remains acceptable therapy for patients in whom this pathogen is isolated (Pfaller et al. 2007).

Candida Glabrata and Candida Krusei—A large portion of these fungi are resistant to azole antifungals. The first line treatment for patients who are infected with this pathogen should be with an Echinocandin such as Micafungin (Bennett 2006).

Candida Auris—this is an emerging multidrug resistant fungal pathogen that is highly resistant to fluconazole. It is still susceptible to Echinocandins but the CDC (Centers for Disease Control) warns that resistance in this organism develops quickly (Centers for Disease Control and Prevention 2018). They currently recommend strict contact precautions and single room isolation in patients who develop infection with this organism. Infection surveillance is now recommended every 3 months. Protocols are likely to change as more information about this pathogen becomes more widely available.

Other Candida Spp.—Candida parapsilosis, tropicalis, lusitaniae, and guilliermondii are other candida species that have been isolated in various critically ill patients. These spp. tend to respond to most antifungal therapy. A notable issue, however, is *that Candida lusitaniae is resistant to amphotericin B but is susceptible to azoles and Echinocandins* (Hawkins and Baddour 2003).

Aspergillus Spp.—Resistance among the Aspergillus spp. is relatively rare but there are isolates that have high resistance to azole therapy (Snelders et al. 2008). In hospitals, geographical areas, or in patients where azole resistant species have been identified, combination therapy with Voriconazole plus an Echinocandin or amphotericin B is recommended.

Histoplasma—Itraconazole is typically first line treatment for this pathogen with amphotericin B being reserved for more severe disease. It is important to remember that Echinocandins have no in vitro activity against histoplasma and they are not recommended for treatment of patients infected with this pathogen (Dismukes et al. 1992). Fluconazole has poor in vitro activity against Histoplasma and is not a recommended therapy.

23.12.2 Special Considerations about Antifungals: Drug Toxicity

23.12.2.1 Azoles

Fluconazole, Voriconazole, and Isavuconazole are the only azoles that have intravenous preparations. All other azoles are only available in oral forms.

The advantage of this class of drugs is that they are generally well tolerated. These drugs are metabolized in the liver by the cytochrome P450 system and thus drug interactions and hepatotoxicity are the common adverse effects of this class of medications. The oral preparations have been known to cause varying degrees of gastrointestinal distress.

Fluconazole has been known to cause reversible alopecia and chapped lips (Pappas et al. 1995).

Itraconazole can cause a triad of hypokalemia, peripheral edema, and hypertension. Cases of ventricular dysfunction have been reported with this medication (Sharkey et al. 1991).

Voriconazole has been known to cause visual disturbances, neurological toxicity which may manifest as visual hallucinations, agitation, myoclonic movements, skin rash, periostitis, cardiac toxicity, and alopecia with or without nail changes (VFEND® I.V. 2018).

23.12.2.2 Echinocandins

These medications are usually well tolerated and are only available in intravenous preparations. Hepatotoxicity is the most common adverse effect out this group of drugs. Other issues include hypersensitivity and infusion reactions and rare cardiac toxicity (CANCIDAS INTRAVENOUS INFUSION 2018; Cleary and Stover 2015).

23.12.3 Amphotericin B

This drug is only commercially available as an intravenous preparation. It is well known to cause toxicities and adverse effects at normal dosages. It can cause infusion reactions that can range from discomfort at the infusion site to hypotension, fever, and chills. Its most common adverse effect is renal toxicity. Electrolyte disturbances and liver dysfunction are also known to occur with amphotericin therapy. (Sawaya et al. 1995)

Amphotericin B is available in various liposomal formulations which does reduce the severity of renal toxicity and other toxic effects. The medication liposomes usually remain intact when they encounter mammalian cell membranes but will degrade when they encounter fungal elements, releasing the medication (Stone et al. 2016).

Given its potential toxicities amphotericin B is not usually first line in treating fungal infections. Due its broad antifungal range, it is still a valuable and sometimes necessary antifungal medication, especially in severe disseminated fungal disease.

23.12.3.1 Flucytosine

This drug has adverse effects primary related to its antimetabolite activity. *High proliferation tissues will be primarily affected* leading to events such as bone marrow suppression, gastrointestinal mucosal breakdown, and alopecia (Guchelaar and Van Kuilenburg 2002). Flucytosine is also known to cause renal and liver dysfunction and can increase the toxic effects of amphotericin B (Stamm et al. 1987).

23.12.4 Future Directions

23.12.4.1 Emerging Diagnostic Techniques

Due to the difficulty in diagnosing fungal infections and the mortality associated with late treatment, there is much research currently into accurately diagnosing these infections. Below we will discuss some of the emerging diagnostic techniques.

23.12.5 Polymerase Chain Reaction (PCR)

The DNA amplification method of using PCR to detect fungal DNA in body fluid specimens is extremely sensitive at detecting fungal DNA. It is also a rapid testing method when compared to culture or pathology techniques. This diagnostic method,

however, is subject to many drawbacks. The method relies on DNA amplification and thus cannot determine microbiological burden or differentiate colonization from real infection. Fungi are ubiquitous and contamination of a specimen can easily lead to erroneous results. Fungi's natural cell wall can make the DNA isolation process difficult due to the chemical methods needed to breakdown the cell to access the nucleic components. As a result of these issues PCR testing is currently not part of any guidelines to implement antifungal therapy and more research will be needed to incorporate this promising diagnostic technique into clinical management of IFI (Arvanitis et al. 2014; Stevens 2002).

23.12.6 Lateral Flow Devices

A point of care testing method for Aspergillus detection. It would function similar to many point of care tests with a control line and positive test line. As of the writing of this chapter, it is still being validated and its commercial availability is still pending (Arvanitis et al. 2014; White et al. 2013).

23.12.7 Candida Albicans Germ Tube Antibody (CAGTA) Assay

This is an immunoflourescent technique that detects antibodies to Candida albicans. It is limited by the fact that candida antibodies may be a normal finding in patients because the fungus is a commensal (Arvanitis et al. 2014; Zaragoza et al. 2009).

23.12.8 Peptide Nucleic Acid Florescent in-Situ Hybridization (PNA-FISH)

This is a cytogenetic technique that uses molecular probes specific for some candida species to more rapidly identify yeasts isolated on blood or tissue culture. This technique only speeds up identification of isolated pathogens and does not assist with antifungal susceptibility testing and is limited by the yield factor of blood or tissue cultures (Arvanitis et al. 2014; Wilson et al. 2005).

23.12.9 Matrix-Assisted Laser Desorption Ionization-Time of Flight Mass Spectrometry (MALDI-TOF MS)

This technique involves measuring the mass to charge ratio of microbiological proteins which is then compared to a database of known pathogenic fungal proteins. This process is rapid, with identification of fungi reported to be as fast as 30 min. It is usefulness is limited not only by the yield of fungi from blood or tissue cultures but by the fact that the proteins from the isolates must be already in the database thereby making it unhelpful if a new fungal isolate is present (Arvanitis et al. 2014; Iriart et al. 2012).

23.13 Summary

- Invasive Fungal infections are associated with significant mortality, particularly when treatment is delayed.
- IFIs represent severe immune debilitation of a patient and patients in the ICU are a vulnerable group.
- There are several risk factors for IFIs and early antifungal therapy is strongly recommended in high risk patients who present with signs and symptoms of sepsis.
- Accurate diagnosis of IFIs is a challenge, the use of adjunctive tests to aid with diagnosis is recommended.
- IFIs due to Candida should be empirically treated with an Echinocandin unless there is good evidence that the candida species will be susceptible to an azole.
- Histoplasmosis should never be treated with an Echinocandin. Itraconazole or Amphotericin B is to be used to treat Histoplasmosis.
- IFIs due to Aspergillus should be treated with Voriconazole or amphotericin B.
- Sinus disease in an immunocompromised host should heavily raise suspicion for IFIs.
- Ophthalmology consultation is strongly encouraged for IFIs to aid with diagnosis and classify severity.
- Our information about IFIs continues to evolve and guidelines and recommendations will continue to be updated as more clinical trials are completed.

A 35-year-old male patient with a history of kidney transplantation is admitted to the intensive care unit after a Graham patch procedure for treatment of a gastric perforation. He is in septic shock and is being treated with Vancomycin and Piperacillin with Tazobactam and his hemodynamics are being supported with Norepinephrine and Vasopressin. He shows no hemodynamic improvement over 48 h despite resolution of his surgical issues and no new identifiable sources of infection.

What are is his risk factors for fungal septicemia?

- Immunosuppression therapy
- Perforated viscus

How would you choose antifungal therapy for this patient?

- Due to the risk of invasive candida and septic shock, initial therapy should be with an Echinocandin. De-escalation to an azole or primary use of an azole can be considered if the risk of azole resistant candida is low.

When should you start antifungal therapy?

- Pre-emptive therapy is recommended and should be started on presentation in this patient with multiple risk factors for fungal sepsis.

What tests could you use to help with diagnosis of an invasive fungal infection?

- A Beta-D-glucan Assay could aid in deciding treatment with an antifungal. A negative test would be highly suggestive of no evidence of fungal infection with candida.

How does his mortality change with an invasive fungal infection?

- His mortality increases to greater than 50% if he does not receive prompt antifungal therapy.

Conflict of Interest No relevant conflicts of interest.

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Pediatric Infections in the Intensive Care Unit (ICU)

24

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24.1 Introduction

The last century has witnessed unmatched advances in understanding of disease processes, surgical skills, and medical technology thereby enhancing our ability to *add years to life*. However, these advances have introduced newer subsets of problems; *infectious complications* related to therapeutic interventions being the most prominent amongst them. They affect both the developed and the developing countries and have a potential to prolong the morbidity and hospital stay, propagate antimicrobial resistance, affect the family economy adversely, and escalate the mortality figures. These *nosocomial, hospital-acquired or health-care associated infections (HAI)* are not present or incubating at the time of admission to the health-care facility (hospital or ICU). It is inherent in the definition of nosocomial infection that the patient was admitted for a reason other than the infection under consideration. Also included within the domain of nosocomial infections are those infections that were acquired during the ICU stay but presented after discharge of the patient and the occupational infections amongst the ICU staff (Benenson 1995). The incidence of nosocomial infections in the ICU patients is 5–10 times higher than that in the general hospital admissions; the toll is even higher for pediatric patients in view of their inherent susceptibility (immature immune system, lack of prior exposure to same or similar antigens, porosity of physical barriers to external invaders, presence of congenital or acquired immunodeficiency disorders, parenteral nutrition for prolonged periods and association with congenital anomalies) (Dasgupta et al. 2015). A study from Europe reported a 25 times higher incidence of nosocomial infections in the neonatal intensive care units as compared to the general children ward (Raymond and Aujard 2000).

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24.2 Neonatal and Pediatric ICUs Vis-à-Vis Adult ICUs

Neonatal and pediatric ICUs are distinct from adult ICUs for several reasons. Firstly, the pediatric ICUs are more likely to be multidisciplinary. This may be related to the lesser number of patients in the pediatric age-group. In fact, it is not uncommon to have the same ICU for both medical and surgical patients even in corporate setups, particularly in the developing countries. Secondly, unlike adult ICUs, it is not yet common to find barriers setup between different beds in a pediatric ICU. Thirdly, a significant proportion of patients being managed in adult ICUs will be suffering from life-style problems or age-related degenerative diseases. Contrarily, most of the patients in pediatric ICUs are expected to lead a normal, productive life after recovery. The primary motto in an adult ICU is death prevention, while that of a pediatric ICU is life-saving. Fourthly, the available data suggest that the risk-adjusted mortality of children managed in adult ICUs is nearly double that of those managed in pediatric ICUs (Coetzee 2005). Fifthly, pediatric critical care is highly cost-effective; the cost per year of saving a life in a pediatric ICU is almost one-tenth of that of an adult ICU. Last on the list, but not the least, the type of skill and knowledge required for a pediatric ICU is significantly different from that required for an adult ICU. A small difference in the age of a child will change the requirements significantly; the post-thoracotomy management of a neonate is different and more challenging than that of a 4-year-old child. In fact, the care of a neonate born at 24 weeks of gestation is different from that of a term baby.

24.3 Epidemiology of Hospital Acquired Infections

The incidence of nosocomial infections in pediatric ICU is more as compared to children admitted in general wards. This is attributed to depressed immunity (both cell-mediated or humoral) and breach in natural defense mechanisms by the therapeutic interventions. According to National Nosocomial Infection Surveillance System (NNIS), the incidence density of these infections is around 14.1 per thousand patient-days (Richards et al. 1999).

In Western literature, the incidence of nosocomial infections ranges from 6.1 to15.1% (Richards et al. 1999) (Urrea et al. 2003). In Indian scenario, the incidence of nosocomial infection in PICU is around 10.5–19.5 per 100 admissions (Gupta et al. 2011; Ahirrao and Mauskar 2017). The infection rates and patterns of predominant organisms also depend on the type of PICU: multidisciplinary, surgical, medical, or cardiac. As obvious, the incidence of infections in a cardiac ICU will be less as compared to others.

24.4 Factors Influencing the Development of Nosocomial Infections

The Microbe as the Causative Agent: Hospitalization comes hand-in-glove with exposure to a multitude of micro-organisms. However, exposure alone is not insufficient. The virulence of the micro-organism, the dose of exposure

(inoculum) and its duration, the drug-resistance status of the microbe and the immune status of the patient, all are important in context. The source of infection could be another patient or a hospital staff (cross-infection), patient himself (endogenous infection) or an inanimate yet contaminated object (fomite-born). More often than not, the causative micro-organism is one which is common in the general population wherein it causes minimal or no harm (such as Staphylococcus aureus, coagulase-negative Staphylococci, Enterobacteriaceae, etc.).

The Susceptibility of the Patient: Certain patients are more susceptible to acquire infections as compared to others depending upon age of patient, immune status, disease processes, diagnostic and therapeutic interventions. Infants and children have inferior resistance to infection as those with malnutrition, chronic illnesses, history of chemotherapy or radiotherapy, and immunodeficiency disorders. Invasion of natural body defense mechanisms by the disease processes or for therapeutic intervention such as biopsy, endoscopic examinations, urinary catheterization, invasive ventilation, repeated suctioning of airways, surgical incisions, etc. also makes the patient susceptible to infections.

Environmental Predisposition: The hospital brings into proximity the patients who are infected, their relatives, and the hospital staff. There are patients infected with virulent or multi-drug resistant strains and those who are immuno-compromised by virtue of age (neonates, geriatric patients, etc.), disease (such as burn patients), or composition (congenital immunodeficiency) under the same roof. The crowding of the hospitals especially the government ones, poor hygiene (if that is the case), transfer of patients across the corridors and the contamination of inanimate objects in the hospital premises, all predispose to nosocomial infections.

Emergence of Multi-Drug Resistant Strains: Development of resistance to antibiotics amongst bacteria is an exponentially emerging health concern in the modern times. Multi-drug resistant strains persist and are known to be endemic inside the hospitals. The magnitude of the problem is even higher in the third world countries where malpractice is rampant, use of antibiotics may not be judicious (Horan et al. 2008; Brissaud et al. 2012), and the affordability of second-line antibiotics may not be universal.

24.5 Spectrum of Micro-Organisms

Organisms causing nosocomial infections can be contracted by exogenous sources or the patient's own flora. Most common nosocomial infections in the pediatric age-groups are the bloodstream infections-HA-BSI (28%) [Hospital Acquired-Blood Stream Infections] followed by pneumonia-HA-VAP (21%) [Hospital Acquired Ventilator Acquired Pneumonia] and urinary tract infection-HA-UTI (5%) [Hospital Acquired-Urinary Tract Infections] (Richards et al. 1999). However, there has been a rising trend in the incidence of HA-VAP. Therefore, HA-VAP is the predominant Hospital Acquired Infection (HAI) in PICU where there is higher utilization of mechanical ventilation (Gupta et al. 2011).

Across the various types of HAIs, 22,323 pathogens in 20,390 HAIs were reported to the National Health-care Safety Network (NHSN) by 1003 hospitals from 2011 to 2014 (Lake et al. 2017). Staphylococcus aureus and

coagulase-negative Staphylococci were the most common of all the pathogens reported, accounting for 17% each; Escherichia coli and Klebsiella pneumoniae/oxytoca accounted for 11% and 9%, respectively. There were 15,538 reports of central line associated blood stream infections (CLABSI); Staphylococcus aureus and coagulase-negative Staphylococci were the most frequently incriminated. One-half of these infections were reported from the NICU, one-fourth from the PICU, and the others primarily from the oncology units and pediatric wards. Catheter associated urinary infections were predominantly reported by the PICUs (83% vis-à-vis 15% from the pediatric wards) with, however, no discrimination in the pathogen spectrum. E. coli was the most common pathogen followed closely by the Pseudomonas aeruginosa.

In India, the most common bacterial micro-organisms isolated from the PICU in healthcare associated infections (bloodstream or pneumonia) include *Acinetobacter* and *Pseudomonas* (Gupta et al. 2011). However, in the USA, the most common micro-organism isolated is coagulase negative-*Staphylococcus* (CONS) species. Similarly, *Pseudomonas* and *Escherichia coli* are common isolates from children with ventilator-associated pneumonia (VAP) and urinary tract infections (UTI) (Richards et al. 1999). *Candida* and *Aspergillus species* are commonly isolated fungi causing invasive infections to children admitted in PICU. *Candida species* constitute the third most common micro-organism causing HA-BSI in children (Brissaud et al. 2012).

24.6 Modes of Transmission

Infections in PICU can be transmitted by direct or indirect contact. Direct contact is transmission from an infected person to susceptible person by actual physical contact. While indirect contact of microbe transmission is through an interim intermediate vehicle or intermediate host like devices, inanimate objects, etc.

Transmission can also be categorized based on the size of the particles—airborne or droplet transmission. Airborne transmission refers to transmission in the form of small particles, i.e., <5 μm. These particles are suspended in air for a long time before entering the susceptible person. Droplet transmission is transmission of microbes in the form of large droplets (>5 μm in diameter). Droplets created by coughing or sneezing is an appropriate example of droplet transmission. These can travel only 1–2 m before entering the susceptible human (Northway et al. 2011).

24.7 Ventilator-Associated Pneumonia

Ventilator-associated pneumonia (VAP) is pneumonia that arises within 48–72 h after initiation of mechanical ventilation (American Thoracic Society and Infectious Diseases Society of America 2005). The Centers for Disease Control and Prevention has defined the condition as pneumonia diagnosed by imaging or by age-specific clinical and laboratory criteria receiving mechanical ventilation for more than 2

calendar days (McBeth et al. 2018). It is the most common cause of HAI after HA-BSIs with reported incidence reaching one-third and rates up to 27.1 per 1000 ventilator-days (Casado et al. 2011; Srinivasan et al. 2009; Bigham et al. 2009; Brilli et al. 2008; Gupta et al. 2015). HA-VAP is associated with high mortality although the associated comorbidities are high and it is not possible to define the attributable risk. Typically, VAP is bacterial and the causative organism is single. However, polymicrobial organisms are on the rise (Jain and Bhardwaj 2018). The most common source of HA-VAP in the PICU is aspiration of the oropharyngeal secretions which are colonized with flora. Besides the oral cavity, micro-organisms are also known to colonize the stomach, upper airways and bronchi; the source of infection may therefore be endogenous or exogenous such as from the contaminated ventilator equipment. The causative organisms are similar in pediatric and adult patients; Staphylococcus aureus, Pseudomonas aeruginosa and gram-negative species such as *Escherichia coli*, *Klebsiella pneumoniae and Acinetobacter* species are the most common (in that order). Viruses such as respiratory syncytial virus and H1N1 are important organisms causing nosocomial pneumonias (Gupta et al. 2011; Lodha et al. 2001). Non-modifiable risk factors predisposing to VAP include endotracheal intubation, gastro-esophageal reflux (GER), tracheoesophageal fistula (TEF) and other airway malformations, malignancies or leukemia, and pre-existent lung pathology. Modifiable risk factors contributing to VAP include multiple intubations, prolonged duration of mechanical ventilation (more than 2 weeks), supine positioning, feeding through nasogastric tubes, use of sedatives and paralytic agents, prolonged antibiotics, use of steroids and H2 blockers (Srinivasan et al. 2009).

The VAP in the pediatric age-groups is distinct from that in adults in view of age-specific comorbidities such as bronchopulmonary dysplasia, hyaline membrane disease, and necrotizing enterocolitis.

A PICU-based prospective cohort study from the authors' institute on patients who were ventilated for more than 24 hours evaluated the incidence, etiology, and risk factors of VAP. In this study, the most common diagnosis for admission was sepsis (16%) followed by pneumonia with acyanotic congenital heart disease (14%). The most common indication for ventilation was respiratory failure (45.3%). VAP was confirmed in 38.4% patients as per the CDC criteria although positive cultures were isolated in only 24.4%. The commonly isolated organisms included Acinetobacter (47%), Pseudomonas (28%), and Klebsiella (15%), in that order (Vijay et al. 2018).

A systematic review focusing on different diagnostic methods and preventive strategies for VAP in the pediatric and neonatal age-groups concluded the lack "gold standard" in literature (Losifidis et al. 2018). The study also highlighted the fact that most of the diagnostic approaches used in these patients have been adapted from the adults.

Other than those who are ventilator-dependent, patients with recurrent seizures or disease processes compromising the level of consciousness are also prone to development of nosocomial pneumonias.

The diagnosis of VAP relies on a meticulous combination of clinical findings (such as temperature instability, change in amount or consistency of secretions, and

oxygen requirement), isolation of pathogens in the respiratory secretions, and radiological evidence of infiltrates. A sensitivity of more than 90% can be achieved by use of Clinical Pulmonary Infection Score (CPIS) incorporating a combination of 6 factors (temperature, white blood cell count, tracheal secretions, oxygenation: PaO2/FiO2 mm of Hg, pulmonary radiography, and culture of tracheal aspirate specimen) (Srinivasan et al. 2009; Zilberberg and Shorr 2010). A correct diagnosis of VAP is crucial to ensure prompt initiation of proper treatment. A delay in treatment leads to an increase in mortality and morbidity. On the other hand, unnecessary treatment with broad spectrum antibiotics will lead to emergence of multi-drug resistant strains.

The management of VAP consists of early institution of antimicrobial therapy. The risk factors for multi-drug resistant pathogens should be kept in mind while making decisions regarding antimicrobial therapy. Broad spectrum cover should be provided for the most common gram-negative pathogens. Piperacillin-Tazobactam, Meropenem, or Imipenem can be considered as empiric regimens pending cultures. Vancomycin should be considered in regions with high incidence of methicillin-resistant *Staphylococcus aureus*.

Apart from initiation of antibiotics, the role of prevention of VAP cannot be overstated. Measures for reduction in incidence of VAP include head-end elevation, use of sedation-weaning protocols, judicious use of antibiotics, avoidance gastric distension and self-extubation, use of cuffed tubes and changing visibly soiled circuits (Joram et al. 2012). These steps when used in conjunction as a *VAP bundle* are known to affect the patient outcomes positively. In an open-labelled randomized controlled trial upon 150 subjects, prophylactic administration of probiotics resulted in reduction of the incidence of VAP in critically ill children (17.1% in the probiotic group vs. 48.6% in the control group) in a setting where baseline VAP rates are high (Banupriya et al. 2015). In the same study, the duration of ICU and hospital stays was reduced by 2.1 and 3.3 days, respectively.

24.8 Central Line Associated Blood Stream Infections (CLABSI)

Central Line Associated Blood Stream Infection represents the most common blood stream infections in children admitted in the PICU. A CLABSI is defined as a laboratory-confirmed bloodstream infection not related to an infection at another site that develops within 48 hours of a central line placement. The diagnosis is established when the same organism is isolated in the blood drawn from catheter as well as blood culture obtained from a peripheral site away from the catheter. *Therefore, a concomitant blood culture from a peripheral vessel is must for the diagnosis and to rule out contamination of the catheter.*

The US-based data estimates the rate of CLABSI at 0.8 per 1000 central line days. However, unlike the VAP, the rates of CLABSI outside ICUs are probably similar to those within ICUs (Zeigler et al. 2015). The NHSN data (2006–2007) has

identified that the most common pathogens associated with CLABSI are gram-positive organisms (coagulase-negative staphylococci @ 34.1% being the most common gram-positive organism) followed by gram-negatives (Klebsiella @ 5.8% being most common gram-negative) and Candida (@ 11.8%) (Atilla et al. 2017; Wright et al. 2018).

The mechanism of CLABSI includes migration of bacteria from the skin surface along the external surface of the catheter tubing. The tunneled catheter with a cuff (which causes a fibrotic reaction around the catheter prevention bacterial migration) is therefore less susceptible to CLABSI as compared to non-tunneled catheters. Contamination of healthcare providers' hands, breach of standard aseptic precautions, and hematogenous seeding from another source, however, may not be overlooked. Host factors such as immunodeficiency states, chronicity of illness, malignancies, ongoing chemo-radio-therapy, malnutrition, burns, etc. also contribute to CLABSI. Pseudomonas infection is seen in association with neutropenia. Candida is common after prolonged administration of broad spectrum antibiotics, hematological malignancy, or solid organ transplantation. Both Pseudomonas and Candida produce extracellular polysaccharide which favors increased virulence and resistance to antimicrobial therapy.

CLABSI exhibits a wide spectrum of clinical manifestations ranging from incidentally detected bacteremia to full blown clinical sepsis. Management of CLABSI includes use of appropriate antibiotics, catheter removal, and prevention of CLABSI using bundled approach along with strict adherence to asepsis protocols. Antibiotics should be guided by the flora prevalent in the ICU and titrated in accordance with the culture reports.

Indications of catheter removal are frank pus at the insertion site, persistence of bacteremia after 48 h of appropriate antibiotic therapy, suspicion of CLABSI in the presence of hemodynamic instability and catheter no longer required (O'Grady et al. 2011). Use of insertion and maintenance CLABSI bundles can lead to significant reduction on the incidence of CLABSI in the ICUs.

24.9 Catheter Associated Urinary Tract Infections (CAUTI)

Health care associated urinary tract infections associated with indwelling urinary tract catheters account for 80% of UTIs (Quinn 2015). Catheter associated urinary tract infections account for more than 12% of hospital infections (CDC 2016). The highest rates of CAUTI have been encountered in the burn ICUs followed by the inpatient medical units and the neurosurgical ICUs (Boev and Kiss 2017).

The source of infection can be endogenous (such as from the urinary meatus, vagina, or the rectum) or exogenous such as contaminated hands of health personnel or contaminated equipment. The infection may be transmitted either extra-luminally (on the surface of the urinary catheter) or intra-luminally (through backflow of urine collected in bag or a break in continuity of tubings somewhere). Formation of a urinary catheter biofilm contaminated with micro-organisms has also been described (Gould et al. 2010).

Commonly encountered pathogens include Escherichia coli (21.4%), Candida (21%), Enterococcus (14.9%), and Pseudomonas aeruginosa (10.0%). The problem of multi-drug resistance is common and expanding with CAUTI too. The CDC (CDC 2016) has defined three mandatory criteria for labelling a patient as having CAUTI: 1) patient with indwelling urinary catheter for at least 2 days on the day of event (day of placement to be counted as day 1) and was either present for any portion of the calendar day on the date of the event or removed the day before the day of event, 2) one of the following symptoms must be present: fever (>38.0 degree C), suprapubic tenderness, costovertebral angle pain or tenderness, urinary urgency, urinary frequency or dysuria, and 3) positive urine culture with no more than two species or organisms identified, one or both of which should be a bacterium ≥15 colony-forming units per milliliter.

Modalities for prevention include avoiding catheterization unless indicated, strict asepsis during catheter insertion, trained personnel to insert catheter, maintaining a closed drainage system, early removal, regular change at fixed intervals if needed for prolonged periods, daily catheter hygiene as per standard recommendations, etc. Role of urinary antiseptics is not yet well-established.

24.10 Surgical Site Infections

The rates of wound infection have decreased drastically over the century with the recognition of the importance of asepsis, use of sterile dressings and aseptic surgical technique (Young and Khadaroo 2014). Yet the Surgical Site Infections (SSI) continue to be a significant concern and leading component for nosocomial morbidity and mortality.

The CDC and NHSN have classified SSIs on the basis of the depth of infection to impart objectivity to reporting of SSIs, assist with surveillance, and monitor quality control measures (Horan et al. 2008; Horan et al. 1992; Rhee et al. 2015).

1. *Superficial Incisional Surgical Site Infection* is one which happens within 30 days of surgery, involves only the skin and subcutaneous tissue and the patient has at least one of the following manifestations: (1) purulent discharge from the incision site, (2) culture positivity of local fluid or tissue, (3) local signs of infection (at least one) such as pain or tenderness, localized swelling, raised temperature, redness, or the superficial incision has been deliberately opened by the surgeon and is culture positive or not cultured, and (4) the diagnosis of SSI has been made by the operating surgeon or the attending physician.
2. *Deep Incisional Surgical Site Infection* is one wherein the infection happens within 30 days of surgery if no implant has been left inside or 1 year of surgery in case of implants and if the infection appears to be related to the operative procedure, involves the deeper tissues of the incision and at least one the following: (1) purulent discharge from the deep incision but not from the organ/ space component of the surgical site, (2) spontaneous dehiscence of deep incision or if it has been opened by the surgeon deliberately and is culture positive/ not cul-

tured with at least one of fever or localized pain or tenderness and, (3) discovery of abscess or other signs of infection upon direct examination, re-exploration, histopathology, or radiology, and (4) diagnosis of SSI made by the operating surgeon or by the attending physician.

3. *Organ/ Space Surgical Site Infection* is one wherein the infection happened within 30 days of surgery if no implant has been left inside or 1 year of surgery in case of implants, if the infection is directly related to surgery or body part manipulated during surgery (excluding skin, fascia, or muscle layers). To qualify for this category, patient must have at least one of the following features: (1) purulent discharge through a drain inside the organ/ space, (2) culture positivity in fluid or tissue from the organ/ space, (3) evidence of infection or abscess formation during clinical examination, reoperation, radiology, or upon histopathology, and (4) diagnosis of organ/ space SSI has been made by the operating surgeon or the attending physician.

The SSI have a direct impact on the patient morbidity and mortality. The incidence of SSI is highly variable with reports from 3% to 20% (Klevens et al. 2007) depending upon a multitude of factors including the type of surgery, immune status, nutritional status of the patient, co-existing infection or colonization locally or remotely, length of hospital stay, and the organizational infrastructure of the healthcare facility. Sometimes, a complication of surgery may initially present as a SSI such as a leak in case of bowel anastomosis closure presenting with pus discharge from the incision site. It is well-known that devascularization of skin flap during hypospadias repair may be inadvertently misinterpreted as wound infection. The CDC has risk-stratified surgical wounds into clean, clean contaminated, infected, or dirty (Mangram et al. 1999). The published results support the fact that the risk of SSI rises with worsening wound stratification (Culver et al. 1991). The spectrum of micro-organisms associated with SSIs has been changing over the decades. We have witnessed a decline in the frequency of SSIs with gram-negative infections with a relative rise in Staphylococcus aureus encounters (Sievert et al. 2013; Hidron et al. 2008; NNIS 1996). Multi-drug resistant strains have become commoner; the most apparent being the rising prevalence of methicillin-resistant Staphylococcus aureus (MRSA) internationally (Jernigan 2004). The role of host microbiome in response to disease is being increasingly recognized especially in the case of inflammatory bowel disease and surgeries for restoration of bowel continuity (Morowitz et al. 2011; Frank et al. 2007; Seksik et al. 2003; Olivas et al. 2012). The role of various peri-operative factors and preventive measures such as skin decontamination, peri-operative warming, and antimicrobial prophylaxis cannot be overemphasized (Mangram et al. 1999; Alexander et al. 2011; Anderson et al. 2008). There have been mixed reports on the use of peri-operative oxygenation and the status is yet to be established (Greif et al. 2000; Belda and Aguilera 2005; Meyhoff et al. 2009; Pryor et al. 2004). SSI rates do not improve with hair removal; however, if the hair need to be removed in view of interference with surgery, it is advisable to remove hair just prior to surgery with a clipper rather than a razor (Mangram et al. 1999; Alexander et al. 2011; Bratzler and Hunt 2006; Tanner et al. 2006).

24.11 Prevention of HAI

A comprehensive approach to reduce the nosocomial infections in PICU is needed. These include adherence to universal precautions, proper hand hygiene of the healthcare professionals, surveillance of HAI, usage of personal protective measures, safe injection practices, screening of the patients and care-givers, etc. (Gupta et al. 2011).

Hand washing/ Hand hygiene between patients is one of the important practices to reduce HAI in the PICU setting. It works by reducing person-to-person transmission. The various factors accounting sub-optimal compliance with hand washing include non-availability of convenient hand washing facility, high staff-to-person ratio, individual allergy to soap, lack of proper knowledge or training, work pressure, paucity of time, temperature of tap-water not ambient to environmental temperature, lack of facilities for drying hands without contamination, etc.

The WHO has identified five key stations for hand hygiene in the clinical setting: before patient contact, before any aseptic technique, after exposure to body fluids, after contact with the patient, and after contact with the patient surroundings (Sax et al. 2007). Hand washing by soap and water for 40–60 seconds is sufficient to remove the viruses. An alternative to hand wash is use of alcohol rubs. Use of alcohol-based rubs for 20–30 seconds is sufficient to remove the micro-organisms. Procedure of hand hygiene should include cleaning all surfaces of the hand. WHO has identified five moments—at which hand hygiene must be followed (WHO Guidelines on Hand Hygiene in Health Care 2009).

Use of laminar air flow ventilation in the operating room and ICUs is helpful in providing high air quality in live conditions and reducing the incidence of SSIs. Laminar air flow ventilated operating rooms reduce the air contamination rates by up to 90% and provide optimal air quality with very low level of colony-forming units close to a surgical wound.

Safe injection practices are necessary to prevent transmission of infections between patients with injections. The recommended measures include eliminating unnecessary injections, use of sterile, preferably disposable needles and syringes, using single dosage vials, adherence to aseptic techniques during injection administration, prevent contamination of medications, and adherence to principles of biomedical waste management including safe sharps disposal after completion of the procedure (World Health Organization 2001).

Good personal hygiene of the hospital staff is a must. Great care should be taken to maintain nails clean and trimmed, hair short and pinned up with clean and trimmed beard and moustache. Dress material should be such that it is easy to wash and decontaminate. A clean dress every day is recommended. Change of outfit if blood- soaked or wet through excessive sweat is a must.

Personal protective measures include devices such as gown, goggles, mask, shields, etc. Paper mask with synthetic material for filtration are known to act as an effective barrier against micro-organisms. The gowns, masks, and gloves are used to protect both the patient and the health-care provider.

All these protective devices will work efficiently only if they are tailored according to size of the healthcare provider (WHO Guidelines on Hand Hygiene in Health Care 2009).

Isolation of patients with high potential for transmission of infection to others or high vulnerability to get infected.

Screening of microbes by performing cultures in admitted patients and healthcare providers is essential. It can help in determining the most prevalent organism (colonizing the patients) in the ICU at a particular time.

Decontamination of the Environment is instrumental in reducing the microbe burden in patient areas in addition to maintaining local/ clinical environmental aesthetics; however, it has not been found to be effective in reducing Healthcare associated infections. Various modalities described include the use of soap water with detergent and hydrogen peroxide or equivalent agents.

Decontamination of the Patient Related Equipment depending upon the risk involved which could be high such as with surgical instruments, moderate as with endoscopes, or mild as in the case of patient bedding. Practice of standard guidelines is highly recommended for decontamination of all patient related equipment.

24.12 Antimicrobial Resistance and Stewardship

With the inadvertent use of empirical antibiotics for suspected sepsis awaiting culture reports, the menace of antimicrobial resistance is growing day-by-day. The current times are witnessing a slow-down in the development of newer antimicrobial drugs almost synchronous with a steep rise in antimicrobial resistance. The increasing prevalence of antimicrobial resistance in both the healthcare and the community settings have become a daunting challenge. The need to adapt to antimicrobial stewardship at a global scale cannot be overemphasized.

Antimicrobial stewardship has been defined as "the optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance" (Gerding 2001). The whole concept aims to work with healthcare professionals to help each patient receive the most appropriate antibiotic in the correct dose and for correct duration while preventing overuse, misuse, or abuse of the same and minimizing development of resistance (Doron and Davidson 2011). This definition also emphasizes the need for inter-professional effort across the continuum of care.

Joseph and Rodvold suggested the "4 D's of optimal antimicrobial therapy": right Drug, right Dose, De-escalation to pathogen-directed therapy, and right Duration of therapy (Joseph and Rodvold 2008).

CDC has defined "*Five rights"* for appropriate antimicrobial therapy: *right antibiotic* (likely organism and its susceptibility; penetration to the site of infection), *right patient* (decision to treat in patients with colonization rather than infection), *right time* (adherence to time-specific administration of the antibiotic such as first

dose within 60 minutes in septic shock bundle, *right route* (switching to oral in patients who can take orally), and *right dose* (correct dose according to age, renal and hepatic clearance).

An important component of stewardship is de-escalation of therapy. This refers to modification of initial empiric regime based on culture reports; broad spectrum to narrow spectrum; combination to monotherapy or stopping therapy altogether. The first steps for successful implementation of stewardship program are understanding problem pathogens and current antibiotic use prevalent in the unit, determine priority areas, and plan intervention by engaging hospital leaders. These programs reduced infection rates with multi-drug resistant bacteria by 51% and MRSA by 37% (Baur et al. 2017). Use of clinical guidelines, treatment algorithms, creating awareness, pharmacodynamic dose optimization, pharmacy based dosing programs, and computer-assisted decision support systems are many other methods when used in conjunction can help to combat antibiotic resistance both at individual level and at global level (Doron and Davidson 2011).

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Antimicrobial Stewardship in Intensive Care Unit

25

Soumya Swarup Ray

25.1 Evolution of Antibiotic Use

Since the discovery of Penicillin by Sir Alexander Fleming in 1928, development of antibiotics has transformed modern medicine. It took over a decade to develop penicillin before it could be used in clinical medicine. It then successfully treated numerous bacterial infections in World War II soldiers and saved many lives. Rapid increase in use of antibiotics was associated with recognition of antibiotic resistance in the 1950s. This resulted in discovery and development of newer beta lactams in the 1960s. The recognition of methicillin-resistant Staphylococcus aureus (MRSA) quickly followed, the first case being recognized in 1962. Carbapenems were first used in the 1980s. This was followed by discovery of carbapenemase producing enterobacteriaceae in the next decade. The emergence of a bacterial strain harbouring resistance has followed release of each new class of antibiotic. The discovery of newer antibiotics has not kept in pace with the increasing prevalence of antibiotic resistance. Very few novel antibiotics have been developed in the last 10 years (Piddock 2012; Ventola 2015).

This has again made bacterial infection a serious threat. Sepsis accounts for a third of admissions to adult general ICUs. Roughly a third of these patients die in the hospital from sepsis, mortality rising to more than 50% in patients with septic shock (Shankar-Hari et al. 2017). Antibiotic resistant infections place substantial health and economic burden on the health care system. This has made antibiotics a precious commodity and emphasizes the need to appropriately use this resource and take steps to retain their effectiveness.

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25.2 Need for Antimicrobial Stewardship in ICU

Intensive care unit is a particularly high-risk environment for use of antibiotics. The prevalence of multi-drug resistant (MDR) pathogens is particularly high in critically ill patients, with significant global variations (Carlet et al. 2004). The risk of having an MDR infection increases with increasing age, increased illness severity, increase in length of stay, prior use of antimicrobials, presence of indwelling catheters (Williams et al. 2009). There is a need to start appropriate antimicrobials early as inadequate initial antimicrobial therapy has been associated with worse outcomes (Liu et al. 2017; Rhodes et al. 2017; Seymour et al. 2017). This results in higher rate of empiric broad-spectrum antimicrobial use in ICU. Up to 70% ICU patients receive antimicrobial therapy on a given day. The average volume of antimicrobial consumption in ICU is almost three times higher than in ward patients with marked disparities in use of broad-spectrum antimicrobials (Bitterman et al. 2016; Versporten et al. 2018). It may be difficult to differentiate a non-infectious cause of fever from an infectious cause in a critically ill patient. Colonization or contamination of the sample can be easily misinterpreted as a true infection and treated accordingly. The high stakes of initial inadequate antibiotic therapy push misuse and overuse of antibiotics. The incidence of unnecessary antimicrobial use can be as high as 30% in hospitalized patients (Hecker et al. 2003). Almost 40% of patients admitted to Australian hospitals in 2015 were prescribed an antimicrobial. Around one-third to one-half of this antimicrobial use was considered inappropriate (Antimicrobial use and resistance in Australia, AURA 2016).

The above data indicate significant room for improvement in antimicrobial prescribing in hospitals and ICU. In this chapter, we will review a few steps to optimize antimicrobial therapy in ICU followed by steps to implement an antimicrobial stewardship programme in ICU.

25.3 Steps to Improve Antimicrobial Usage in ICU

25.3.1 Rapid Identification of Critically Ill Patients with Bacterial Infection

Sepsis can be difficult to diagnose in critically ill patients with multiple comorbidities. Temperature abnormalities are common in ICU patients. Up to 50% episodes of fever can be non-infectious in origin. Fever at presentation was not associated with any significantly increased risk for death in this study (Laupland et al. 2012). Traditional microbiological cultures take time and are frequently negative in clinically infected patients.

The Sepsis-3 task force emphasizes the presence of organ dysfunction to diagnose sepsis and recommends the use of quick sepsis-related organ failure assessment score (qSOFA) as a bedside tool to diagnose sepsis (Singer et al. 2016). Patients with suspected infection who are likely to have a prolonged ICU stay or to die in the hospital can be promptly identified by the qSOFA score which includes

presence of alteration in mental status, systolic blood pressure ≤100 mm Hg or respiratory rate ≥22/min. However, the evidence of whether qSOFA helps to rationalize antibiotic therapy is lacking so far.

Biomarkers can be useful to rule out bacterial infection in critically ill. C reactive protein (CRP) and procalcitonin (PCT) are the two biomarkers in common use. Serum CRP is an acute phase protein synthetized by the liver. It has a sensitivity of 68–92% and a specificity of 40–67% as a marker of bacterial infection (Cho and Choi 2014). PCT is a propeptide of calcitonin, a hormone involved in calcium and phosphate homeostasis. Its synthesis is triggered by bacterial endotoxin and inflammatory cytokines from inflamed infected tissues and neuroendocrine cells. It has a sensitivity of 77% and a specificity of 79% for early diagnosis of sepsis in critically ill patients (Cho and Choi 2014). Procalcitonin has been better studied in critically ill. In patients with community-acquired pneumonia and a serum procalcitonin (PCT) level less than 0.25 ng/mL, the likelihood of an invasive bacterial aetiology is less than 5%. Normal serum PCT level eliminates a bacterial aetiology of the shock in more than 95% of patients (Gilbert 2017). However, in a recent single centre prospective randomized trial a PCT guided algorithm, despite increasing the number of withheld treatments did not result in reduction of antibiotic consumption, did not shorten time to adequate therapy or improve patient outcomes. The ability of procalcitonin to differentiate between certain or probable infection and possible or no infection, upon initiation of antibiotic treatment, was low (Layios et al. 2012). PCT is currently not recommended as a tool to decide initiation of antibiotics in the surviving sepsis guidelines (Rhodes et al. 2017).

A host of novel biomarkers like sTREM-1(soluble triggering receptor expressed on myeloid cells-1) suPAR(soluble urokinase-type plasminogen receptor), ProADM(proadrenomedullin), PTX3(pentraxin-3) are currently in development and may have important diagnostic and prognostic value in sepsis and may be useful in antibiotic management of sepsis.

In the absence of any gold standard tests, the clinicians still have to rely on their clinical judgement in addition to the available laboratory test and clinical tool like qSOFA to decide whether to initiate or withhold antimicrobial therapy. Delaying antibiotics in haemodynamically stable patients till more objective results are available may be a useful strategy in select patients.

25.3.2 Identifying High Risk Patients for MDR Infections

In the majority of patients in ICU, empiric therapy is started before microbiological culture and antibiotic sensitivity results are available. It is important to identify the patients at a high risk of having an MDR pathogen to use appropriate broad-spectrum antibiotics in these critically ill patients with organ dysfunction.

Colonization increases the risk of subsequent infection with an MDR pathogen. Less than 10% of patients in ICU are colonized by methicillin-resistant Staphylococcus aureus (MRSA) at admission. MRSA colonization is associated with a more than eight-fold increase in the risk of associated infections during ICU

stay, and MRSA infection develops in one-fourth of patients who are colonized with MRSA at admission to the ICU (Ziakas et al. 2014). Extended-spectrum Beta-lactamase-producing Enterobacteriaceae (ESBL-E) infections occur during the ICU stay in 10–25% of ESBL-E intestinal carriers (Zahar et al. 2018). However, positive predictive value of a colonizer causing an infection remains less than 50%, irrespective of the colonizer (Timsit et al. 2019). The risk of having an MDR infection also increases with increasing age, increased illness severity, increase in length of stay, prior use of antimicrobials, presence of indwelling catheters (Williams et al. 2009). Geographic location, socioeconomic status, patient population group also significantly influence risk and type of MDR pathogens and their susceptibility, highlighting the need to develop local guidelines.

25.3.3 Optimize Dose of Antibiotic Therapy

Effectiveness of an antibiotic depends on the ability of the antibiotic to penetrate infected tissue in sufficient concentration, in excess of the minimal inhibitory concentration (MIC) of the bacteria. Antimicrobials can be described by their killing mechanism into concentration dependent (aminoglycosides, quinolones) or time dependent (β-lactams, macrolides, oxazolidinones). For concentration dependent killing, it is important to have peak concentration/MIC >8–10 and 24-h area under the concentration curve (AUC)/MIC >100–125. For time dependent killing it is important to keep the blood concentration above MIC, most of the time between the doses (Roberts et al. 2014a).

Critical illness causes significant changes in antibiotic pharmacokinetics. Fluid resuscitation, presence of chronic liver or renal disease, extracorporeal organ support, renal replacement therapy increase the volume of distribution of the drugs. Hyperdynamic haemodynamic state in sepsis increases the clearance, whereas liver and renal dysfunction can reduce clearance of antibiotics. Because of these changes, antibiotic dosage for critically ill patients based on data from general patient population is likely to be suboptimal. In a prospective multicentre point prevalence study across 68 hospitals, blood levels of beta lactams were found to be below the minimal concentration target in one out of six patients. Positive clinical outcome was associated with increasing time of concentration above the MIC in the same trial, with significant interaction with sickness severity status (Roberts et al. 2014b).

In view of above data, it is important to ensure critically ill patients are receiving optimal antimicrobial dose. This is more important early in the clinical course, when maximal drug effect is desirable. Volume of distribution of most antibiotics (especially hydrophilic antibiotics) is frequently increased in most critically ill patients. Hence the first dose may need to be increased and it should not be adjusted to renal function in patient with renal dysfunction. Therapeutic drug monitoring (for vancomycin, teicoplanin, aminoglycosides) can be useful to avoid both under dosing and overdosing.

25.3.4 Early Microbiological Diagnosis

Traditional microbiological testing usually involves gram staining, cellular analysis of bodily fluids, culture and in vitro susceptibility testing of different specimens. Gram staining and cellular analysis results are readily available in a few hours and can be helpful in guiding therapy. Raised white cell count and present of nitrite and leucocyte esterase in urine can be suggestive of urine infection. Although it is highly sensitive, positive predictive value of simple urinalysis was shown to be only 45% in a single centre study of female patients presenting to emergency department (Leman 2002). The positive predictive value increases when both nitrite and leucocyte esterase are positive. Positive predictive value may be poorer in catheterised ICU patients. More importantly, a negative urinalysis has a much higher negative predictive value for a urine infection (Simerville et al. 2005). A negative urinalysis reliably excluded a catheter-associated urinary tract infection in the febrile, trauma ICU patient with a 100% negative predictive value (Stovall et al. 2013). Cellular analysis of bodily fluid (cerebrospinal fluid, ascitic fluid, joint fluid) can be useful in suggesting infection. The shape and staining pattern of bacteria on Gram stain can be helpful in guiding initial empiric antimicrobial therapy. However, a positive Gram stain, in case of suspected ventilator-associated pneumonia (VAP) correlated poorly with recovery of the organism in culture with only 40% positive predictive value in this meta- analysis (VAP prevalence was 20–30% in the individual studies). Negative predictive value of Gram stain was 91% in the same meta-analysis, suggesting that VAP is unlikely with a negative Gram stain (O'Horo et al. 2012)

Identification of pathogen on culture usually takes 2–3 days and the susceptibility testing may take further 2–3 days. This results in prolonged empiric antibiotic therapy for many ICU patients. Empiric antibiotics were continued for more than 4 days in nearly 60% of patients without adjudicated nosocomial infection in this multicentre prospective cohort study (Aarts et al. 2007).

Due to the above limitations with traditional microbiologic tests, there is increasing interest in development of novel tests for rapid pathogen identification and their sensitivity pattern. Automated polymerase chain reaction (PCR) based systems are currently available which allow rapid detection of MRSA, vancomycin resistant enterococci (VRE), resistant gram-negative bacteria. They can be used directly on the clinical sample saving time. One limitation of this approach is that the presence of resistance genes may not always correlate with phenotypic resistance. Quantitative real time PCR can be used on previous culture to look at genome copy numbers for differentiating susceptible from resistant strains. Unlike the PCR based approach, this indirectly measures phenotypic resistance by detecting growth in the presence of antibiotic. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) can be used for the rapid and automated identification of pathogens and detection of resistance. Microarray technology allows detection of numbers of different resistance genes in a single assay. Microfluid platforms require very small volumes of analyte, can be highly automated with potential for providing rapid results. Because of their small size, they may be used for point of care

antimicrobial susceptibility testing. In future, whole genome sequencing would allow identification of all bacterial pathogens and their resistance pattern from a clinical sample. Currently, the usage of these modalities is limited by cost, availability and clinical validation trials. Many of these rely solely on detection of resistant determinants. The question of discordance between the presence of a resistance determinant and phenotypic resistance needs to be answered prior to their widespread clinical use (Cisneros et al. 2013).

25.3.5 De-escalation

De-escalation has been defined as a strategy to reduce both the spectrum of antimicrobial therapy and the selective pressure on microbiota (Weiss et al. 2015). It includes switching from combination to monotherapy. Antimicrobial therapy is reviewed in 48–72 h, as soon as the antimicrobial sensitivity results become available. Antimicrobials could be ceased if infection is deemed unlikely.

However, de-escalation was used in only about half of the patients with bacterial infection in this systematic review (Weiss et al. 2015). It was more frequently performed in patients with broad-spectrum and/or appropriate antimicrobial therapy, when more agents were used, in the absence of multidrug-resistant pathogens, with lower or improving severity scores. It did not show any adverse effect on patient outcome or mortality. However, there was no reduction in antibiotic days with antibiotic de-escalation (Tabah et al. 2016)

In view of low prevalence of de-escalation and its potential impact on rise in antimicrobial resistance, cost and increasing side effects, efforts should focus on microbiological documentation to increase physician confidence and compliance with de-escalation. Newer diagnostic tools which hasten pathogen identification and susceptibility testing would be useful. Negative cultures are found in about a third of patients with sepsis. In view of risks of continued unnecessary antimicrobial therapy, surviving sepsis campaign recommended thoughtful de-escalation of antimicrobials based on adequate clinical improvement even if cultures were negative (Rhodes et al. 2017).

25.3.6 Shortening Duration of Antimicrobial Therapy

Prolonged antibiotic therapy has been consistently associated with development and dissemination of antimicrobial resistance (Goossens 2009). This is also associated with increase in side effects and secondary infections like fungal infections, Clostridium difficile colitis. Shorter courses of antibiotics are known to be safe and effective in many different infections. A multicentre randomised trial in patients with ventilator-associated pneumonia showed comparable clinical effectiveness with the 8- and 15-day treatment regimens (Chastre et al. 2003). Among patients with possible VAP but minimal and stable ventilator settings, very short antibiotic courses (1–3 days) were associated with similar outcomes to longer courses

(>3 days) (Klompas et al. 2017). The STOP-IT trail on patients with intraabdominal infections who had undergone an adequate source control procedure showed similar outcomes after fixed-duration antibiotic therapy of approximately 4 days compared to a longer course of antibiotics of approximately 8 days that extended until after the resolution of physiological abnormalities (Sawyer et al. 2015). Two recent meta-analyses showed comparable outcomes with shorter courses of antibiotics in common infections like community-acquired pneumonia, ventilator-associated pneumonia, intraabdominal infections, skin and soft tissue infections, uncomplicated cystitis, and complicated cystitis or pyelonephritis, without any adverse events (Hanretty and Gallagher 2018; Royer et al. 2018). Current guidelines strongly recommend a 7 day course of antimicrobial therapy for nosocomial pneumonias (Kalil et al. 2016). However, short courses of antibiotics may not be advisable in all patients, especially those with inadequate source control, infection with MDR organisms, fungal infection, immune- deficiency, endovascular infections or slow clinical response (Rhodes et al. 2017).

25.3.7 Importance of Source Control

Source control includes identification of the focus of infection and all physical steps taken to eliminate a source of infection, control ongoing contamination and to restore premorbid anatomy and function (Marshall and al Naqbi 2009). This may include debridement of infected necrotic tissue, drainage of infected fluid collection, removal of infected device and often deferred restoration of normal anatomy and function.

Efficacy of source control may be time critical. Delay in source control (just like delay in antimicrobial therapy) has been associated with poor outcomes. Time to initiation of surgery in hours was significantly associated with 60-day outcome in patients with gastrointestinal perforation associated with associated septic shock (Azuhata et al. 2014). Time from diagnosis to surgical treatment >14 h in patients with septic shock were independently associated with hospital mortality in ICU patients with necrotizing soft tissue infections (Boyer et al. 2009). Surviving sepsis guidelines recommends a target of no more than 6–12 h after diagnosis for most cases (Rhodes et al. 2017). Potentially infected intravascular devices should generally be removed promptly after establishing another site for vascular access. Adequate microbiological analysis should be performed on the samples obtained from the infected source.

The benefit of optimal source control procedure needs to be balanced against the potential risks of the procedure (stress of surgery, potential time delay, risks of bleeding, complications, risk of transfer for the procedure, likelihood of success). Minimally invasive surgical or drainage procedures may be preferable to open surgical procedures in critically unwell patients when the diagnosis of the source is certain. The decision about the type of source control procedure should be individualised depending on the risk vs benefit to the patient and institution specific logistic factors. In patients with persistent or new organ dysfunction despite resuscitation

and appropriate antimicrobial therapy, failure of source control should be considered. Repeat imaging and source control intervention should be considered in such cases.

25.4 Antimicrobial Stewardship Programme (ASP)

Antimicrobial stewardship has been defined as a coherent set of actions which promote using antimicrobials responsibly (Dyar et al. 2017). Infectious Diseases Society of America has described it as a set of coordinated interventions designed to improve and measure the appropriate use of antimicrobial agents by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy and route of administration (Fishman 2012). It can be seen as a quality improvement programme consisting of development of institutional policy, an interdisciplinary team (members typically consisting of Infectious Diseases physicians, Pharmacists and Intensivists in ICU), clear definition of goals, indicators, and targets, continuous monitoring and surveillance with feedback to prescribers, identification of areas of improvement and filling in quality gaps. Successful antimicrobial stewardship programs are multidisciplinary, and operate within an organisation's governance systems with the support of the organisation's executive.

25.5 Evidence for ASP

Most of the studies on antimicrobial stewardship have focussed on development of antimicrobial resistance and reduction of unnecessary usage of antimicrobials. Cochrane review in 2017 found that interventions to improve prescribing were effective in increasing compliance with antibiotic policy and reducing duration of antibiotic treatment. Lower use of antibiotics probably did not increase mortality and likely reduced length of stay (Davey et al. 2017). In a metanalysis by Karanika et al., ASP resulted in nearly 20% reduction in total antimicrobial use in hospital (twice as much reduction in ICU) and nearly 34% reduction in cost. It was associated with decrease in infection due to MDR organisms without any increase in adverse outcomes (Karanika et al. 2016). However, the previous 2017 Cochrane review reported an inconsistent effect on resistant gram-negative and gram-positive bacteria, citing too few studies and too much variance in microbial outcomes (Davey et al. 2017). ASPs have consistently demonstrated a decrease in antimicrobial use (22–36%), with annual savings of $200,000–$900,000 to the hospital (Dellit et al. 2007). Although many studies on ASP do not show a change in patient centric clinical outcomes, they reassuringly do not also show adverse clinical events (Tabah et al. 2016; Lesprit et al. 2015; Singh et al. 2000). However, unintended complications have been reported with isolated ASP. Change from cephalosporins to gentamicin for surgical antibiotic prophylaxis in Scottish hospitals was associated with significant increase in acute kidney injury (Bell et al. 2014).

25.6 General Elements of ASP

The different antimicrobial stewardship interventions can be classified into three broad categories (Timsit et al. 2019).

Restrictive	Collaborative	Structural
Reduce opportunities for bad behaviour, increase barriers	Increase opportunities for good behaviour, decrease barriers	Systematic steps to improve antimicrobial usage
• Formulary restriction • Mandatory prior authorisation by senior ASP doctor • Automatic stop order	• Development of institution specific antimicrobial guidelines • Prescriber education • Promote de-escalation • Prospective audit and feedback to prescribers • Easy availability of antimicrobial resources	• Faster diagnosis of antimicrobial resistance • Antibiotic consumption audit • ICU leadership commitment • Stewardship rounds with collaboration between ICU physician, ID physician, pharmacist • Use of information technology

25.7 Core ASP Approaches

- Formulary restrictions limit the initiation of unnecessary or inappropriate broad-spectrum antimicrobial by restricting its availability and requiring prior authorisation for its release. This may include development of approval code to allow usage of antimicrobials. Restriction of ciprofloxacin was associated with a decreased resistance of Pseudomonas aeruginosa isolates to antipseudomonal carbapenems and ciprofloxacin in a tertiary teaching hospital's intermediate care and intensive care units (Lewis et al. 2012). Care must be taken to avoid any potential delays in therapy and mitigate any concerns about loss in prescriber autonomy.
- Automatic stop orders ensure regular review of patient medication regimens to help avoid potential toxicity or emergence of resistant organisms to antibiotics. It prevents unnecessarily prolonged therapy and reduces drug costs. Steps must be taken to prevent inappropriate and/or inadvertent premature stopping of Antimicrobials.
- Development of institution specific antimicrobial guidelines, based on national guidelines, local antibiogram and availability of antimicrobial agents can improve antimicrobial utilization. They should include guidelines for common infections and surgical prophylaxis regimes.
- Regular education of health care providers (doctors, nurses and pharmacists) on ASP principles will facilitate implementing the programme and increase compliance. Nursing staff should be aware of the need to start prescribed antibiotics early and to avoid missed doses. They should feel empowered to question a prescription which does not fit in with local guidelines. Junior doctors should be aware of the principles of rapid diagnosis and treatment of a bacterial infection,

steps to minimize development of resistance and the importance of de-escalation. Pharmacists can ensure that the antimicrobials are dosed appropriately and adverse events are recognized early. They can help in development of formulary and ongoing audit.

- Leadership commitment at the ICU level as well as hospital level is crucial to the success of the stewardship program. Collaboration between ICU physicians and the infectious diseases physicians and pharmacists will improve governance of the programme. This may include regular antimicrobial stewardship rounds in ICU, sharing of antimicrobial usage and antimicrobial resistance data.
- A standardized prospective audit and feedback method is an effective way to ensure that antibiotics are used appropriately. This may include review of all antimicrobial prescriptions and their compliance with local guidelines on a prespecified day, overall usage of different classes of antibiotics, incidence of MDR organism isolates. This could be followed up over time and compared to national database. Feedback is provided to prescribers recommending changes or discontinuation of antimicrobial, key antimicrobial outcomes are reported regularly to the prescribers.
- Health care information technology (IT) in the form of electronic prescribing, and clinical decision support systems can enhance decision-making. Antimicrobial prescription resources and guidelines can be made easily accessible to the prescriber.

25.8 Conclusion

In this era of rising antimicrobial resistance and limited development of new antibiotics, ASP can improve patient care and reduce development of antimicrobial resistance without any increase in adverse clinical outcomes. Institution specific needs, resources and priorities need to be considered when designing an ASP. Ultimate success of ASP depends on strong leadership and executive support, interdisciplinary team work, education and feedback.

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Principles of Infection Prevention and Control in ICU

26

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26.1 Introduction

Prevention of infection in ICU setting is very difficult and needs multidisciplinary approach to monitor and control it. Even after increasing awareness among health-care workers (HCWs), WHO-estimated worldwide hospital-acquired infection rate is 7–12% (Mukhopadhyay 2018). The major infections of concern are central line associated blood-stream infection (CLABSI), ventilator-associated pneumonia (VAP), catheter-associated urinary tract infection (CAUTI), clostridium-difficile induced colitis, surgical site infection (SSI) or infected decubitus ulcer, etc. increasing resistant micro-organisms due to prolonged unnecessary use of broad-spectrum antibiotics without dose adjustment, lack of following the protocols of isolation and hand hygiene with general preventive measures, failure to maintain surveillance strategies are major factors for failure to control infections in ICU. Here we will discuss all the preventive measures one by one.

26.2 General Measures

26.2.1 Hand Hygiene (WHO's -5 Moments of Hand Hygiene) (The WHO Guidelines on Hand Hygiene in Health Care 2009)

Two moments before touching a patient to protect the patient from harmful germs carried on hand of HCWs and patient's own germs

1. Before touching a patient
2. Before aseptic procedures

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Three moments after touching a patient to protect oneself and health care environment from harmful patient's germs

1. After touching a patient
2. After body fluid exposure
3. After touching the patient's surrounding

Hand-wash protocol (The WHO Guidelines on Hand Hygiene in Health Care 2009)

1. *If hand is visibly dirty with blood or body fluid*—after wetting all surfaces of hands and fingers with plane water and applying soap, hand should be scrubbed for at least 15 s. Then hands should be thoroughly dried using disposable towel.
2. *If hand is not visibly dirty*—hands should be rubbed with solution containing 0.5% chlorhexidine (CHD) and 70% w/v ethanol. This combination covers gram-positive, gram-negative bacteria, virus, fungi, and mycobacteria. CHD also has residual activity.
3. *Before hand washing for any aseptic procedure, all hand jewelries should be removed* (Table 26.1).

26.2.2 Other Protective Measures: (Mehta et al. 2014)

Patient-care equipment: Used patient-care equipment like laryngoscope, bougie, stylet, bronchoscope, etc. soiled with body fluids and secretions should be handled carefully to prevent spread of infection to other patients, HCWs, and environment and should not be reused without proper cleaning and sterilization. Single-use items including sharps should be discarded strictly.

26.3 Modes of Infection Transmission and Prevention

Micro-organisms can be transmitted by airborne, tiny droplets or large droplets, and by direct contact.

- *Transmission through direct contact*—transmission in ICU mainly occurs by contaminated hands of HCWs. Hands are directly contaminated either from patients' infected body area or from inanimate objects around patient (Table 26.2).

26.3.1 Airborne and Droplet Transmission

Airborne transmission: Droplet nuclei with <5 μm in size remain suspended in the air for long periods and can travel long distance. (Mukhopadhyay 2018; Guidelines n.d.)

Table 26.1 showing indication of gloves, gown, and other protective barriers for protection from infection

	Sterile	unsterile	Comments
Gloves	Should be worn- • When performing sterile procedure (e.g. central line, arterial line, Foley's catheter, etc.) •Shouldberemoved-As soon as gloves are damaged • Before answering telephone or recording patient notes, etc.	Clean, unsterile gloves should be worn- • For touching blood, body fluids, contaminated items and any infectious materials	• Gloves should be changed between touching two patients and even in same patient while moving from contaminated to clean body area • Gloves should be removed as soon as possible after care of a patient • Hand hygiene should be practiced strictly after removal of gloves
Gown	Require only for aseptic procedure	Clean, non-sterile gown is safe for any procedure other than aseptic one, especially to prevent soiling of clothes and skin rom blood, body fluids, secretions, and excretions	*Soiled* gown should be removed as soon as possible to prevent the spread of infection
Mask, face-shield			Face-shield should be worn to prevent eyes and nasal mucosa from the exposure of blood, other body fluids, secretions, and excretions when there is chance of splashing. Masks should be worn always in ICU to prevent spread of respiratory infection

*Droplet transmission***:** Infective micro-organisms are transmitted in the form of large particles (>5 μm in size) during coughing, sneezing, and talking or during invasive procedures such as bronchoscopy, pleural tap, endotracheal intubation, tracheal suctioning, etc. (Mukhopadhyay 2018; Guidelines n.d.) (Table 26.3).

Modes of transmission for waterborne infections include (Guidelines n.d.)

1. Direct contact (e.g. hydrotherapy).
2. Ingestion of contaminated water (e.g. consumption of contaminated iced water).
3. Indirect contact transmission (improperly processed medical device).
4. Inhalation of aerosols dispersed from water sources or respiratory therapy equipment.
5. Aspiration of contaminated water (Table 26.4).

Table 26.2 showing micro-organisms spread through contact transmission and its prevention (Russotto et al. 2015; Bhattacharya 2006)

Vehicle of contact transmission	Micro-organisms	Prevention method
HCWs' hand Bedrails ECG leads Blood-pressure cuffs Ventilators (button, circuits) Suction system Medical chart Ultrasound machine Stethoscope White-coats Cell-phones Hand washing sink Computer keyboard	*Gram-positive bacteria* Methicillin resistant Staphylococcus aureus (MRSA) Methicillin sensitive Staphylococcus aureus (MSSA) Coagulase-negative staphylococci Vancomycin resistant enterococci (VRE) Clostridium difficile *Gram-negative Bacteria* Acinetobacter baumannii Pseudomonas aeruginosa Klebsiella spp. Extended-spectrum beta-lactamase (ESBL) Carbapenem resistant Enterobacteriaceae (CRE) *Viruses* Varicella (chicken pox) Respiratory syncytial virus (RSV) Herpes zoster Hepatitis A Rotavirus	Private room preferred, cohorting allowed if necessary General measures of hand washing, gown and gloves to be followed Risk of environment contamination to be minimized during patient transport (e.g. Patient can be placed in a gown) Non-critical items should be dedicated for use of a single patient only Active surveillance to search out the asymptomatic careers of multi-drug resistant organisms (MDRO) so that they can be isolated Surface cleaning (walls, tables, etc.) twice weekly, floor cleaning 2–3 times daily. Thorough and more frequent terminal cleaning of patient bed area including bedrail, mattress during stay and after discharge, or death with environmental protection agency (EPA) registered disinfectant Non-critical equipment (e.g.- stethoscope, blood-pressure cuff, dialysis machine, defibrillator, ventilator, thermometer, medication area, table, etc.) require cleaning followed by disinfection by low-intermediate disinfectant [e.g. Ethyl alcohol or isopropyl alcohol in concentrations of 6090% (v/v)] (Rutala 1996)

26.4 Bundle Care

Bundle is a group of evidence-based care components for a given disease that, when executed together, may result in better outcomes than if implemented individually.

26.4.1 VAP Bundle (Wip et al. 2009)

- Head elevation at 30–45 ° (semi-recumbent position) (LOE IA)
- Twice daily oral care with chlorhexidine solution (LOE IA)
- Daily sedation vacation if feasible and assessment of readiness to extubate (LOE IA)

The other strategies to prevent VAP (Wip et al. 2009)

Table 26.3 showing spread of common micro-organisms through airborne and droplet transmission and their preventive measures (Bhattacharya 2006; Guidelines n.d.)

	Airborne infection	Droplet infection
Organisms	*Common Bacteria* Mycobacterium tuberculosis Bacteria atypically causing airborne transmission *Staphylococcus aureus* (mainly transmitted through contact or droplets. Airborne dispersal of S.aureus directly associated with concentration of bacteria in anterior nares. 10% healthy career disseminate in air. Usually recovered from operating room, ICU, burn units, and neonatal ICU) *Group A beta hemolytic streptococci* (mainly transmitted through contact or droplets. Outbreaks of surgical site infection have been traced from operating room personnel to patients. Usually recovered from operating room, ICU, burn units, and neonatal ICU) *Bacillus spp* (can survive long period in air due to capability of spore formation) *Acinetobacter spp* (only gram-negative bacteria which withstand inactivating effects of drying) *Viruses* Measles virus (rubeola) Varicella-zoster virus (VZV chicken pox) Herpes zoster (shingles) Rubella virus Swine flu (H1N1) Influenza virus *Fungi* Aspergillus spp. Mucorales (Rhizopus spp)	*Bacteria* Hemophilus influenzae (meningitis, pneumonia) Neisseria meningitidis (bacteremia, meningitis, pneumonia) Mycoplasma pneumonia Group A streptococci Staphylococcus aureus Bordetella pertussis *Virus* Influenza virus Adenovirus Rhinovirus Corona virus
Preventive measures	Patient should be placed in a monitored negative pressure room with at least 6–12 air exchanges per hour. Room exhaust must be appropriately discharged outdoors or passed through high-efficiency particulate aerator (HEPA) filter before recirculation within hospital Disposable N-95 mask should be worn by all persons entering room. Susceptible subjects should not enter room ideally Transport of the patient should be minimized. If it is unavoidable, patient should be masked	Private room preferred. Cohorting allowed if necessary Everyone should wear mask (ideally N-95) while entering isolation room or within 6–10 ft. of the patient. Transport of the patient should be minimized. If it is unavoidable, patient should be masked

- Endotracheal tubes with subglottic suction port is preferred to prevent microaspiration (2A)
- Avoid intubation and re-intubation whenever possible (2B)
- Closed endotracheal suction systems may be better than open suction (2B)
- Consider non-invasive ventilation whenever possible (2B)

Table 26.4 showing spread of micro-organisms through the contaminated environment and their preventive measures (Guidelines n.d.)

Bacteria	Contaminated environmental vehicle	Preventive measures
Legionella spp.	Aspiration of contaminated water or inhalation of contaminated aerosol (cooling tower, faucets, respiratory therapy equipment, room-air humidifiers, etc.)	Cold water should be stored and distributed at temperature <20-degree C. Hot water should be stored above 60-degree C and circulated with a minimum return temperature of 51 degree C (American Society of Heating 2000). Near point-of-use preset thermostatic mixing valve should be added and maintained periodically to prevent burn. Additional chlorine and flushing of water (American Society of Heating 2000; Snyder et al. 1990)
Pseudomonas aeruginosa Burkholderia cepacia Stenotrophomonas maltophilia Sphingomonas spp.	Distilled water Contaminated disinfectant Contaminated mouthwash Dialysis machine Nebulizers Ventilator temperature probe Water bath	Separate sink for hand washing and disposal of contaminated fluids (Ayliffe et al. 1974) Dialysate should be ≤2000 cfu/mL Water should be ≤200 cfu/mL (Favero and Petersen 1979) Ice and ice machine should be cleaned periodically. Open storage compartment in patient area is avoided (Newsom 1968). Sterile water should be used in ice bath (Pien and Bruce 1986). Transfusion products should be wrapped in protective plastic wrap during temperature modulation in germicide added water bath (Muyldermans et al. 1998) All patient equipment should be dried after sterilization. Residual moisture in the working channels (e.g. endoscope, bronchoscope) must be dried through alcohol rinse or forced air drying (Humphreys and Lee 1999). Disinfection solution should be changed frequently Humidifier and nebulizer should be cleaned and sterilized in low temperature
Serratia marcescens	Contaminated antiseptic (e.g. chlorhexidine) Contaminated disinfectants (glutaraldehyde and quaternary ammonium compounds)	
Acinetobacter spp.	Medical equipment that collect moisture (e.g. ventilator, humidifier, vaporizers, etc.) Environmental surface Room humidifier	
Enterobacter spp.	Intravenous fluids Rubber piping of a suction machine Blood gas analyzer Unsterilized cotton swab Humidifier water	
Non-tubercular mycobacteria (NTM)	Inadequately sterilized medical equipment Dialysis, reprocessed dialyzers Contaminated disinfectant solution	

- Monitor endotracheal cuff pressure (to be kept >20 cmH_2O) to avoid air leaks around cuff (2B)
- Ventilator circuits should not be changed routinely (2B)
- Heat moisture exchanger is better than heated humidifier (2B)
- Any condensate collected in the tubing should be discarded (2B)

26.4.2 Central Line Bundle (all LOE IA) (The Joint Commission 2013)

- Femoral route for central venous cannulation should be avoided. Upper extremity should be preferred for insertion. If on emergency basis femoral cannulation must be done, it should be removed as soon as crisis period is over and replaced with jugular or subclavian vein cannulation.
- Maximal sterile barrier precautions (cap, mask, sterile gown, sterile gloves) should be taken and full-body should be covered with sterile drape during central venous catheter (CVC) insertion.
- Skin should be cleaned with 2% chlorhexidine with 70% w/v ethanol followed by drying for at least 30 seconds before CVC insertion.
- Sterile, transparent, semipermeable dressing should be used to cover the catheter site and it should only be replaced while it becomes damp or soiled or get loosened.
- Need of CVC should be assessed daily and should be removed as soon as possible when it is not required.

26.4.3 Other Strategies to Prevent Central Line Associated Blood-Stream Infection (CLABSI) (The Joint Commission 2013)

- Ultrasound-guided insertion should be in protocol if machine and expertise are available.
- Catheter insertion site should be checked and palpated daily through dressing for any tenderness.
- Patients' body should be cleaned daily with 2% chlorhexidine wipe to reduce CLABSI.
- Needleless intravascular catheter access system should be used, and stopcock should be avoided. Closed catheter system should be preferred to open system.
- Injection port should be cleaned with chlorhexidine, povidone-iodine, or 70% alcohol every time during injection and should be accessed only with sterile device.
- Routine replacement of CVC is not required.
- Administration sets including add-on devices (e.g. triway) should be replaced daily in patients receiving blood, blood products, or fat emulsions.

- In case of intravenous fluids other than blood or blood product, administration set should not be replaced <96 h and should be changed at least every 7 days.
- Needleless connectors should be changed every 72 h.

26.4.4 Strategies to Prevent CAUTI (Parida et al. 2013)

- Catheter should be inserted only when it is indicated really and should be removed as soon as possible when there is no requirement.
- Asepsis should be followed during insertion (sterile gloves, sterile draping, and proper cleaning.
- Closed drainage system should be maintained. For unobstructed flow of urine, catheter should be placed and taped above the thigh and urinary bag should hang below the level of bladder.
- Urobag should never be in contact with floor.
- As it is closed system, changing indwelling catheters or drainage bags at fixed interval is not recommended. It should be changed only if there is indication like infection and obstruction or when closed system is compromised.

26.5 Environmental Control

26.5.1 Design of Intensive Care

(a) Intensive care unit should be adjacent to operation theater (OT) complex and emergency department or easy and rapid accessibility of sick patients. It should be away from general ward for prevention of infection.
(b) Proper heating, ventilation and air conditioning (HVAC) system should be established and monitored periodically for proper function. HVAC system is designed to
   - Maintain indoor air temperature and humidity at comfortable levels for patients and staff.
   - Remove contaminated air.
   - Protect patients and susceptible staffs from airborne pathogens.
   - Minimize risk for transmission of airborne pathogens from infected patients (Streifel 1999).

1. *HVAC system includes (in sequence)(*American Conference of Governmental Industrial Hygienists (ACGIH) 2001*):Outside air inlet → filters* [low efficiency (20–40%) filter has low resistance to airflow and it removes large particulate matter and many micro-organisms allowing smaller particles to pass onto air-conditioning coils](Streifel 1999) → *Humidity modification equipment* [temperature is maintained within 20–23 degree C and humidity is maintained between 40 and 60% above which is an independent risk factor for fungal

growth(American Institute of Architects 2001). Recirculated air is also added in this chamber] → *High-Efficiency Particulate Air (HEPA) filter* [99.97% efficient for removing particles ≥0.3 μm diameter. It is mandatory to use in positive pressure isolation room for immunocompromised patients and operating rooms designated or orthopedic implant procedures to prevent airborne infection (Aspergillus spores are 2.5–3.0 μm in diameter)](Streifel 1999) → *FANS* → *Registers/ Diffuser/ Griller*(for proper distribution of conditioned air) → *Ductwork* [After distribution of conditioned and filtered air, a portion of air is returned through this duct system to be delivered back to HVAC unit for getting diluted with outside air and again filtered through HEPA filter] → *Air exhaust* [after returning through duct system, rest of the air is exhausted. Air from toilet or other soiled areas is usually exhausted directly to atmosphere through separate exhaust].

Any malfunction or damage of any of the above-mentioned components leads to outbreak of airborne and droplet infection in ICU. So, regular monitoring and surveillance of these components are very important.

2. *Ventilation*—According to guideline, Air-Change per Hour (ACH) must be >12 in positive pressure area or protective environment (PE) where immunocompromised patients are kept and treated. In negative pressure area or Airborne Infection Isolation (AII) room, ACH should be ≥12 in renovated or newly constructed ICU after 2001 and ≥6 in ICU constructed before 2001. Peak efficiency for particle removal in the air-space occurs between 12 and 15 ACH (Streifel 1999; Memarzadeh and Jiang 2000).
3. *Laminar* airflow ventilation system is designed to move air in a single pass, usually through HEPA filters either along a wall or ceiling, in one-way direction through a clean zone in parallel stream. Uni-direction flow minimizes air-turbulence, thus precipitation of micro-organisms and spores. Airflow rate of 0.5 m/s minimizes proliferation of micro-organisms. It is important in PE room to reduce airborne healthcare-associated infection. (Walmsley et al. 1993).
4. *Pressurization*—Isolation should be with both positive and negative pressure ventilation. There should be at least 1 isolation room for every 6 beds in ICU. In PE room ideal pressure differential is > +8 Pa and in AII room pressure differential must be < −2.5 Pa. Pressure differential is the difference between isolation unit and adjacent room or hall or corridor. (Streifel 1999; American Institute of Architects 2001).
5. Air movement must be always from clean to dirty area.
6. Adequate space around each bed in ICU should be there (2.5–3 m or 20 m^2).
7. Washbasins should be installed between every other bed.
8. Alcohol gel dispensers should be at the ICU entry, exit, every bed space, and ventilator.
9. Separate medication preparation area. It should be >3 ft. away from wash basin.
10. There should be separate areas for clean storage and soiled and waste storage and disposal.
11. Electricity, vacuum, or air outlets should not hamper access around beds.
12. Appropriate location of sharps.

13. Seamless floors and avoiding use of carpets (wet carpet helps in growth of micro-organisms and during cleaning it releases micro-organisms and spores).

26.6 Antibiotic Stewardship

Antimicrobial stewardship program is a multidisciplinary approach which includes clinical pharmacist, clinical microbiologist, infection control professionals, and hospital epidemiologists. With active participation of microbiology lab, hospital pharmacy, and finally hospital administration, this program will be successful. The goal of this stewardship is as follows:

- To decrease unnecessary use of antibiotics, thus decreasing cost.
- To prevent antibiotic resistance by decreasing inappropriate use of antibiotics.

The different ways to achieve this goal are as follows: (The Core Elements of Hospital Antibiotic Stewardship Programs n.d.)

1. Regular audit of antimicrobial use with direct interaction and feedback by antimicrobial stewardship program senior member.
2. Continuous education and discussion about advancement in prescription, guidelines of dosing, de-escalation, etc. should be practiced in health-care setting. In this discussion all physicians and paramedical staffs should be present.
3. Institutional guidelines should be established based upon evidence of local microbiological data and resistance pattern. In this way, antibiotics can be utilized in better way.
4. After culture sensitivity report is available, immediate de-escalation of antibiotic is strictly recommended and must be practiced. Audit should be done on de-escalation practice.
5. Knowledge of pk/pd. characteristics of antibiotics should be shared during discussion so that optimal dosing of antibiotics is practiced.
6. Close vigilance on appropriate dosing, active use of information technology (hospital information system) to track electronic medical record, computerized physician order entry can improve the antibiotic stewardship program.
7. Antimicrobial cycling and combination therapy to prevent emergence of resistance is not recommended as these are not found to be essential.
8. Early switching from parenteral to oral antibiotic when parenteral antibiotic is no longer indicated, especially in resource limited setting to decrease cost of therapy is recommended.

9. Optimization of duration of antibiotics should be followed as per latest clinical guidelines. It decreases cost of therapy, unnecessary antibiotic consumption as well as side-effects. It should be actively incorporated in program.
10. Use of microbiology lab should be optimal.

26.7 Maintenance and Surveillance

Environmental disturbance during construction, renovation, or repair in or near ICU significantly increases Aspergillus spore count in indoor air. Sudden outbreak or cluster of cases increases suspicion of environmental source to be culprit. In case of construction work, patients should be relocated to another temporary ICU area.

All water-damaged materials should be replaced, if moist materials are not dried within 72 hours, those should be replaced (Vujanovic et al. 2001). Fungistatic compounds should be incorporated into building material in area at risk of getting high moisture. All windows of ICU should be sealed. Door should be closed as much as possible. Entry should be restricted for visitors to reduce dust intrusion and infection transmission.

26.7.1 Air Sampling

- Both particulate sampling and microbiological sampling are done.
- In particulate sampling the numbers and size range of particulates are known, thus it indirectly evaluates the efficiency of filter in removing respirable particles (<5 μm diameter). Particle count in ICU or operation room should be evaluated against counts in comparison area, like corridor, ward, etc. It helps to have information about the ICU air quality and control of dust dispersion (Streifel 1999).
- Though colony or spore count is not significantly correlated with infection rate in ICU, microbiological air sampling is done nowadays as part of epidemiological investigation in case clusters. Molecular typing can determine whether isolates from air matches with patient isolates or not (especially in case of aspergillosis). At least 1000 ml or 1 m^3 air should be sampled from ICU (Thio et al. 2000). It is considered that 15 CFU/m^3 gross colony count of fungal organism and < 0.1 CFU/m^3 of Aspergillus fumigates and other opportunistic fungi in HEPA filtered area are the maximum limit to prevent infection (American Institute of Architects 2001).
- Air sampling is done after construction or renovation of ICU, especially of isolation rooms and then periodically.

26.7.2 Water Sampling and Prevention of Infection (Guidelines n.d.)

- Analysis should be done using standard quantitative methods for endotoxin in water used to reprocess hemodialyzers and for heterotrophic and mesophilic bacteria in water used to prepare dialysate and for hemodialyzer reprocessing.
- To minimize growth and persistence of gram-negative waterborne bacteria, cold water should be stored and distributed at temperature below 20-degree C and hot water should be stored above 60-degree C with minimum return temperature 51 °C thermostatic mixing valve is installed near point of use.
- Addition of additional chlorine in the water.
- All water systems should be inspected annually to ensure proper function of the thermostats.

26.7.3 Maintenance and Repair of HVAC System (Guidelines n.d.)

- HVAC system should not be shut down regularly without any purpose like maintenance or filter change, etc. as during starting machine it suddenly releases micro-organisms (e.g. Aspergillus spore) in huge amount accumulated in system.
- Regular manometer test to ensure the pressure differential in positive and negative pressure areas.
- Regular Testing of Filters- HEPA filter efficiency is especially monitored with dioctyl phthalate (DOP) particle test using the particles sized 0.3 μm diameter. Low-medium efficiency filters are also tested regularly (Dryden et al. 1980).
- Low-medium efficiency filter should be changed frequently to prevent dust build-up on HEPA filter.
- Regular cleaning of ductwork vents should be done. Filter should be replaced as per need and the replaced filter should be disposed into plastic bag immediately to prevent potential exposure of patients and staffs as HVAC system is shut down at that time.
- Air intake system should be kept free from bird droppings as much as possible to minimize the concentration of fungal spores in entering air.
- Temperature and humidity of the air should be regularly monitored. Excessive humidity and moisture accumulation in HVAC system can increase proliferation of fungi (Aspergillus, etc.) and bacteria (Pseudomonas aeruginosa, Staphylococcus aureus, Acinetobacter spp. etc.) causing significant spread of nosocomial infection in ICU. Water is present in cooling units and humidifying boxes. Duct system also can create conditions of high humidity and excess moisture.

26.8 Special Concerns for Specific Pathogens

Micro-organism	Risk-factors + major mode of transmission	Recommendation for prevention	Role of environmental sampling
1. MRSA 2. Vancomycin intermediate staphylococcus aureus (VISA) 3. Vancomycin resistant enterococci (VRE)	1. Colonized patient in ICU 2. Medically high-risk patients (e.g.- long stay in ICU) 3. Multiple and/or prolonged broad-spectrum antibiotics 4. Immunosuppressed patient like post-transplant Major mode of transmission is through health care workers' contaminated hand through direct patient contact, bedrails, bed-linens, gowns, tables, bedside and computer table, medical equipment, etc.	1. Strict adherence to hand hygiene. 2. Cohorting of patient 3. Direct patient-care items should be disposable whenever possible especially during managing patient with multiple-resistant micro-organism (Layton et al. 1993) 4. Routine cleaning and disinfection of house-keeping surface and patient-care area with low-intermediate level disinfectants like, alcohol, sodium hypochlorite or quaternary ammonium compounds at recommended dilution and adequate contact time (Byers et al. 1998)	Routine environmental sampling is not required, yet laboratory surveillance of environmental surface should be done during suspected episodes of contamination or outbreak and renovation or construction. For MRSA, nasal swab and swab from hand web are taken from HCWs for culture. For other organisms, swab from hand web are taken
Clostridium difficile	1. Antibiotic therapy, mainly beta-lactam antibiotics 2. Gastrointestinal procedures and surgery 3. Advanced age. 4. Indiscriminate use of antibiotics Transfer of the pathogen to the patient via the hands of health-care workers is thought to be the most likely mechanism of exposure (Fekety et al. 1981). Hand is contaminated through direct infected patient or patient-care items and bed area	1. All the above-mentioned preventive measures 2. Restriction of use of antimicrobial agents (Johnson et al. 1992) 3. Environmental cleaning with specific chemical germicide (chlorine containing chemicals like 5000 ppm sodium hypochlorite 1:10 v/v dilution or phosphate-buffered hypochlorite 1600 ppm	

According to literature, three new technologies seem to be successful to disinfect the ICU environment even in inaccessible areas (Blazejewski et al. 2011)

- Hydrogen peroxide vapor.
- Ultraviolet light decontamination for terminal cleaning.
- Ultramicrofibers associated with copper-based biocide for daily cleaning.

26.9 Education of Health Care Workers and Monitoring

- Continuous classes (both classroom and bedside) to educate the health care workers is one of the most important strategy to have success in control of infection in ICU.
- Pictures, animations, and videos are good options through which knowledge of good hygiene and consequences of infections can be shared very rapidly.
- Feedback should be taken from HCWs.
- Close monitoring of hand-hygiene practice is single most important factor to reduce infection in ICU significantly.
- Incidence and prevalence data of all types of infection in ICU are to be sincerely collected and analyzed and based upon which annual/biannual audit should be done.

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Point-of-Care Testing in Intensive Care Units

27

Nitin Gupta

27.1 Introduction

Increase in the role of diagnostics in patient management has created an urgent need for point-of-care (POC) testing with rapid turnaround time. POC tests are largely based either on immunochromatography (ICT) or polymerase chain reaction (PCR) assays. These tests are extremely useful in order to make rapid decisions which may help make a diagnosis in a patient that needs to be isolated or make a diagnosis in a patient that requires some specific treatment. The role of POC testing in intensive care unit is discussed in this chapter with emphasis on tropical fevers, respiratory infections, neurological infections, and gastrointestinal infections.

27.2 Characteristics of an Ideal Point-of-Care Test

1. Do not need specialized laboratories or staff with much technical expertise
2. Easy to use and interpret
3. Rapid turnaround time (within 1–2 h)
4. Cheap and cost-effective
5. Sensitive and specific

27.3 Types of POC Tests

There are two main types of POC tests: immunodiagnostic and molecular (Table 27.1)

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Table 27.1 Summary of types of point-of-care tests

Type of POC	Advantages	Disadvantages	Examples
Immunodiagnostic point-of-care tests (Drancourt et al. 2016)	• No need for a power source, maintenance, or training. • Test is easy to transport and store due to its small size. • Usually resistant to variations in temperature	• May have low sensitivity (usually between 60% and 95%) • Visual interpretation of results is operator dependent	Malarial antigen detection
Molecular point-of-care tests	• Greater sensitivity than the ICT	• Require a higher degree of technicality and training • Some reagents may require temperature controlled environments for storage • More expensive	Cartridge based nucleic acid amplification (GeneXpert) for tuberculosis

1. *Immunodiagnostic POC tests:* These tests are usually based on the principle of immunochromatography (ICT). These tests are available in form of strips (horizontal or vertical flow assay) which detects antigen or antibody present in the clinical specimens with the help of a corresponding antibody or antigen conjugated to gold or a fluorescent marker (Fig. 27.1).
2. Molecular POC Tests
   (a) PCR-based techniques: PCR is a method of amplification of target DNA (or RNA after reverse transcription) which requires the use of thermocycler for various steps such as denaturation, annealing, extension, and amplification. This is followed by the detection step in which the amplified DNA is detected. Real-time PCR (RT-PCR) is a variant of PCR where amplification and detection are done simultaneously. It additionally has a step where a fluorescent probe is hybridized to the target DNA, thereby increasing the specificity.
   (b) Loop mediated isothermal amplification (LAMP): LAMP is a cheaper alternative to PCR assays as it does not require thermocycler.

27.4 POC in Acute Febrile Illness (Tropical Fever)

The presentation of various tropical fevers may be overlapping and it is often difficult to distinguish them clinically. Early diagnosis and rapid initiation of treatment is extremely important to prevent mortality in critically ill patients (Table 27.2).

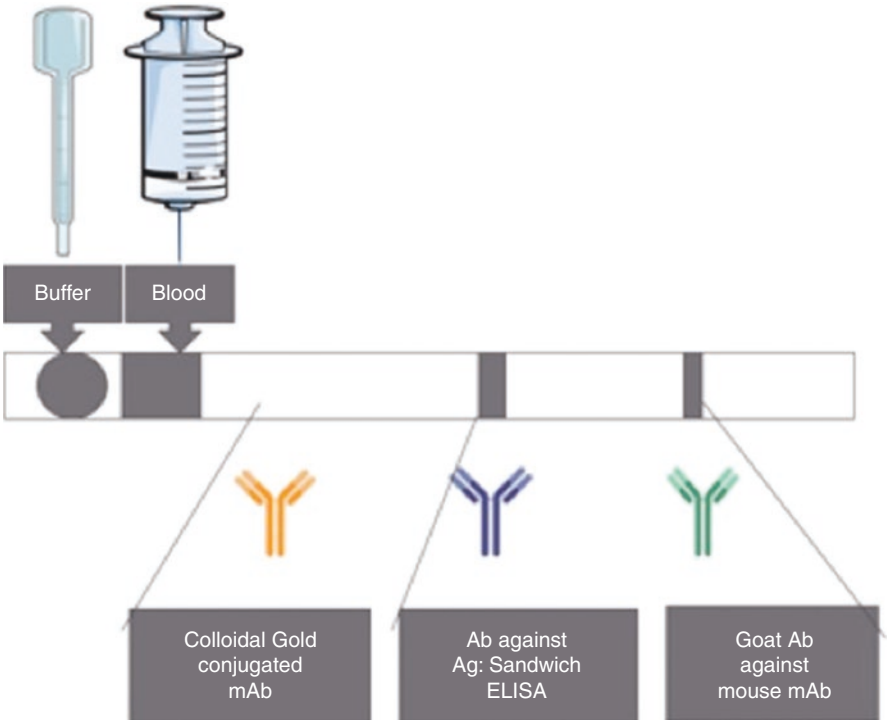

Fig. 27.1 Overview of an Immunochromatography based point-of-care test

Table 27.2 Summary of point-of-care tests for tropical fevers

Tropical fever	Antigen or antibody detection	Sensitivity	Specificity
Malaria (Mathison and Pritt 2017)	Antigen	Depends on parasite species and density	99.6%
Dengue (Drancourt et al. 2016)	NS1antigen	38–71%	76–80%
	IgM antibody	30–96%	86–92%
Leptospirosis (Niloofa et al. 2015)	IgM antibody (Leptocheck)	78–93.8%	84.5–98%
Scrub typhus (Gupta et al. 2017)	IgM antibody (Inbios)	87%	100%
Enteric fever (Wijedoru et al. 2017)	Antibody (Typhidot)	84%	79%

27.5 POC in Lower Respiratory Tract Infection

Rapid diagnosis in patients with lower respiratory infection requiring intensive care is extremely important because it not only helps in initiating specific treatment but also tells about the need and type of isolation precautions to be employed (Table 27.3).

Table 27.3 Summary of point-of-care tests for lower respiratory tract infections (LRTI)

LRTI	Type of test	Sensitivity	Specificity
S. pneumoniae	Urinary antigen	50–80%	>90%
Legionella pneumophila (Drancourt et al. 2016)	Urinary antigen	99%	74%
Influenza (Drancourt et al. 2016)	Antigen	60%	100%
	Real-time PCR (Cepheid)	97.8%	100%
Tuberculosis (WHO 2019)	Real-time PCR (Cepheid), GeneXpert	98% in smear positive 68% in smear negative	99%

Table 27.4 Summary of important studies on procalcitonin guided antibiotic therapy

S/n	Study particulars	Methodology	Results
1	Christ Crain et al. (2004)	243 patients with LRTI- impact of PCT guided therapy	47% reduction in antibiotic use No difference in clinical outcomes
2	Burkhardt et al. 2010)	550 patients with mild LRTI- impact of PCT guided therapy	Reduction in antibiotic use No difference in clinical outcomes
3	Shehabi et al. (2014)	400 patients with bacterial sepsis- impact of PCT guided therapy	No significant reduction in antibiotic use No difference in clinical outcomes
4	PBC-PCI study (2014)	422 samples, utility of PCT in predicting blood culture positivity	PCT levels significantly higher in blood culture positive patients
5	De Jong et al. (2016)	1546 patients with suspected infection- PCT based discontinuation	Decrease in antibiotic consumption and mortality
6	Bloos et al. (2016)	1089 patients with septic shock/ severe sepsis- PCT based discontinuation	Decrease in antibiotic consumption but no significant difference in mortality
7	DPUP study (2016)	453 patients, utility of PCT in diagnosis of pneumonia and differentiating with heart failure	Sensitivity-80%, Specificity-77%
8	Huang et al. (2018)	1656 patients with LRTI- role of PCT guided therapy	No significant difference in terms of antibiotic days and adverse outcomes

It should be noted that there are some POC tests that may not detect the pathogen but may help in indicating presence or absence of an infection. Procalcitonin levels can be measured at the POC in order to assist medical decision-making regarding the prescription of antibiotics for respiratory tract infections. Procalcitonin levels of 0.5 mg/mL of blood may indicate a possibility of bacterial infection. A fall in procalcitonin levels from the baseline is deemed more significant as it can be used reliably for de-escalation or discontinuation if antibiotics (Schuetz et al. 2017) (Table 27.4).

Multiplex panels like respiratory Film Array Panel system (BioFire; bioMérieux) are expensive but have been useful in making a quick diagnosis. A total of 22 pathogens can be detected within an hour. An agreement of 99.2% was noted with the comparator in an analysis (Leber et al. 2018).

27.6 POC in Neurological Infections

The timing of antibiotic therapy is extremely important factor that determines outcome in patients with meningitis. POC tests are therefore extremely important in making a rapid diagnosis. One of the most useful tests in this context is detection of cryptococcal antigen detection test in patients with human immunodeficiency virus infection (Vidal and Boulware 2015). Detection of the polysaccharide antigen in CSF is extremely sensitive and specific in making a diagnosis of cryptococcal meningitis. Both latex agglutination and lateral flow assay formats are available. Latex agglutination tests have also been found to be useful in making a diagnosis of pyogenic meningitis. The sensitivity of these tests varies from 50 to 100% in gram stain or culture positive samples (Paliwal and Tejan 2018). GeneXpert and its newer version 'Ultra' have shown to be useful for diagnosis of TB meningitis. Multiplex panels similar to the one described in the LRTI section are also available for neurological infections as well (Leber et al. 2016). Novel applications of point-of-care technologies such as use of glucometer for rapid estimation of glucose in CSF have resulted in shorter turnaround time. In a recent study from France, a cut-off of 0.46 for CSF/blood glucose ratio calculated by a glucometer yielded a sensitivity and specificity of 94% and 91%, respectively (Rousseau et al. 2019).

27.7 POC in Gastro-Intestinal (GI) Tract Infection

Although POC tests for multiple GI pathogens (Rotavirus, Adenovirus, Campylobacter spp., *Entamoeba histolytica*) are available, in critical care settings, *Clostridium difficile* is the single most important pathogen that requires early diagnosis and prompt initiation of therapy. Rapid detection of *C. difficile* toxins A and B in hospitalized patients with nosocomial diarrhea can be done using POC tests. They have a sensitivity and specificity of 90% and 99.5%, respectively (Lübbert et al. 2014). RT-PCR assays (GeneXpert) are also available for toxin detection in patients with antibiotic associated diarrhea (Granato et al. 2018).

Several studies have shown the cost benefit analysis of routine use of point-of-care testing. While these tests are extremely useful in intensive care settings where decision taking cannot be delayed while waiting for the conventional test results to return, caution is advised that the sensitivity and specificity of that particular test should be checked while interpreting the results.

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Sepsis in Chronic Liver Disease

28

Abhinav Anand and Shalimar

Key Points

- Infections are common in patients with chronic liver disease
- Infections can lead to clinical presentation as liver failure and multi-organ failure, which in turn lead to poor outcomes
- Early recognition of sepsis and appropriate treatment with antibiotics is essential to improve the survival
- Regular surveillance for infections is essential for early diagnosis

28.1 Introduction and Definition

The spectrum of chronic liver disease includes chronic hepatitis, cirrhosis, hepatocellular carcinoma. The clinical presentation ranges from compensated stable cirrhosis to decompensated cirrhosis and acute on chronic liver failure (ACLF). The etiology of cirrhosis is multifactorial, and each cause has its own pathophysiological mechanism for liver damage; often multiple etiologies may co-exist in a particular patient. Patients with alcoholic hepatitis/autoimmune hepatitis are often on corticosteroids with or without other immunosuppressants, making them more susceptible to infections.

Patients with cirrhosis are nutritionally deficient due to decreased dietary intake and have an accelerated muscle breakdown to compensate for the nutrient deficiency. In the natural course of cirrhosis, the occurrence of complications—like variceal bleeding, hepatic encephalopathy, acute kidney injury, ascites—also predisposes to the development of infections. Infections are associated with four-fold higher mortality rates among patients with cirrhosis. The heterogeneity in the

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severity of liver disease, the varying etiologies with their treatment options, and an impaired immune response refute the "one size fits all" approach for the management of sepsis in patients with cirrhosis.

Cirrhosis is associated with impairment of the immune system secondary to the loss of immune surveillance and reduced synthesis of pathogen recognition receptors. A systemic inflammatory response occurs in response to the translocation of bacteria or bacterial products from the intestinal lumen. Both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) contribute to the inflammatory response. The abnormalities in the immune function and systemic inflammatory response (defined as cirrhosis-associated immune dysfunction) predispose to infections.

28.2 Epidemiology/Problem Statement

Bacterial infections are present in 32–34% of patients with cirrhosis who undergo hospitalization. The risk further increases to 45–60% in patients who present with a gastrointestinal bleed. The rates of nosocomial infections are also high, ranging from 15–35%. Bacterial infections are even more common in patients with acute on chronic liver failure. Nosocomial infections are more prevalent, with studies showing that up to 65% of patients with acute on chronic liver failure develop an infection during their hospital stay. The presence of active infection is a contraindication for a liver transplant, which may be a life-saving measure among decompensated cirrhosis.

The infections which are commonly seen in patients with cirrhosis include spontaneous bacterial peritonitis (SBP) (25–30%), urinary tract infections (20–25%), pneumonia (15–20%), skin and soft tissue infections (11%), and bacteremia (10–12%). The most common community-acquired pathogens include gram-negative Enterobacteriaceae (*E. coli, Klebsiella* species) and gram-positive bacteria (*Enterococci* and *Staphylococcus aureus*). Gram-positive organisms are more common in patients with recent hospitalization, receiving quinolones for SBP prophylaxis and after invasive procedures.

Healthcare-acquired infections are the infections detected within 48 h of hospital admission in patients with any prior contact with healthcare in the previous 90 days. Nosocomial infections are infections diagnosed after 48 h of hospital admission. Not only are these infections common in patients with cirrhosis, but they are also often caused by drug-resistant organisms (64%) and are associated with higher mortality. The common causative organisms include extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae*, *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA), and *Enterococcus fecium*. Multi-drug resistant organisms are seen in up to 4% of patients with community-acquired infections, 14% in healthcare-associated infections, and in 35% of patients with nosocomial infections. With the increase in the use of broad-spectrum antibiotics, invasive procedures and hospitalizations, the prevalence of drug-resistant organisms are expected to be on the rise. This will not just confer a poor prognosis; it will initiate a perpetual cycle for the use of more broad-spectrum antibiotics.

Fungal infections are not uncommon in patients with cirrhosis and acute decompensation. A recent series reported prevalence to be around 14.7% among patients with acute on chronic liver failure. High Child–Pugh–Turcotte score, invasive procedures and prolonged duration of hospital stay make individuals more susceptible to fungal infections. What complicates the scenario is the low index of suspicion, non-specific symptoms, absent definite diagnostic definitions, lack of standardized tests, low detection along with prolonged incubation period of cultures, and difficulty in invasive sampling. To make matters worse, colonization is difficult to distinguish from infection, especially when samples are obtained from non-sterile sites. The common etiological agents include *Candida albicans*, non-albicans *Candida* species, and *Aspergillus* species. Patients with fungal peritonitis have very high mortality: 56–90%. Hence, fungal infections must be considered in patients with liver cirrhosis, especially in the subgroup with above-mentioned risk factors and those not improving despite antibiotic therapy.

28.3 Pathogenesis

The pathogenesis of sepsis in cirrhosis is multifactorial and involves gut microbiota, pathological bacterial translocation through increased intestinal permeability, and immune dysfunction. The relationship between the systemic inflammatory response syndrome (SIRS) and infection leads one to hypothesize that an inflammatory response may lead to immune dysregulation, which may predispose the patient to an infection that would then aggravate a marked pro-inflammatory response, resulting in a vicious cycle. This immunopathology in patients of cirrhosis is reminiscent of the multimodal immunological response classically noted in patients with severe sepsis, which is typified by an initial SIRS response followed by a compensated anti-inflammatory response (CARS). The mechanisms associated with this phenomenon are not elucidated, but immune paresis has been postulated as a possible mechanism. The risk of bacterial infection increases with the severity of liver disease as suggested by the higher model for end-stage liver disease (MELD) score and Child–Pugh–Turcotte (CTP) score. Among patients with acute on chronic liver failure, the risk of infection increases with the higher grades suggesting that the higher the number of organ failures, greater is the risk of infection. The other prognostic scores which have been used for predicting the outcome in patients with cirrhosis include acute physiology and chronic health evaluation (APACHE) II score and the recently described CLIF Consortium ACLF score (CLIF-C ACLF). Maddrey's discriminant function (DF) is derived for patients with alcohol as etiology. The higher these scores, greater is the severity of the disease and the higher the risk of infections and sepsis.

The risk of bacterial infections also depends upon the etiology of the precipitating event, which leads to decompensation of the chronic liver disease. An increased frequency of infection is seen among patients who are actively consuming alcohol, as compared to those who get superinfection—hepatitis E virus or reactivation of hepatitis B virus. Therefore, it is essential to simultaneously manage both—the sepsis and the underlying cause of liver disease.

28.4 Gut Microbiota

Alteration of gut microbiota in patients with cirrhosis is both quantitative (bacterial overgrowth) and qualitative (dysbiosis). Bacterial overgrowth occurs secondary to decreased intestinal motility, modulation of acid secretion, altered constituents of bile and use of anti-microbial medications. Reducing the burden of intestinal bacteria has shown to decrease infectious disease complications in patients with advanced cirrhosis.

28.5 Diagnosis of Sepsis

Systemic inflammatory response syndrome is paramount for the diagnosis of sepsis. Unfortunately, its applicability in patients with cirrhosis is doubtful. Patients with cirrhosis are often on beta blockers, this coupled with elevated bilirubin may impair elevation in heart rate. A total leucocyte count within the normal range may not indicate the absence of infection in cirrhotic patients, who also have hypersplenism.

On the contrary, hepatic encephalopathy, tense ascites, hyperdynamic circulation, and leucopenia due to hypersplenism may lead to a diagnosis of SIRS in the absence of infection. The prevalence and relevance of asymptomatic infections are also unclear. Thus, suspecting a diagnosis of sepsis based entirely on signs and symptoms would be wrong. Early detection and diagnosis of sepsis are critical. Hence there is a need for newer tools.

Regular surveillance of infection with blood, urine, endotracheal aspirate among patients on a ventilator are useful for early identification of organisms. It is essential that samples are collected before the start of antibiotics.

28.6 Markers of Inflammatory Response

C-reactive protein (CRP) and procalcitonin (PCT) are biomarkers commonly used for early detection of sepsis. CRP is produced mainly from the liver; PCT is produced from multiple organs (lung, kidney, liver, adipose tissue) in response to bacterial endotoxins or inflammatory mediators such as interleukin (IL)-1β, IL-6, and tumor necrosis factor-alpha (TNF-α). The serum levels of these markers are not different in patients with cirrhosis as compared to the general population. A recent meta-analysis showed that procalcitonin has a useful role as a diagnostic test with a high positive likelihood ratio (7.38). CRP, on the other hand, is good to rule out a bacterial infection with a negative likelihood ratio of 0.23 in patients without signs of infections. The combination of CRP and PCT has a better predictive value in the identification of infections than CRP alone. Despite the promising evidence, PCT-based algorithms for the initiation or discontinuation of antibiotic therapy are still lacking for patients with cirrhosis.

28.7 Early Identification of Pathogens

Conventional bacterial culture is time-consuming. Real-time polymerase chain reaction (PCR) assays enable rapid detection of bacterial and fungal pathogens with sensitivity similar to standard culture. Unfortunately, frequent identification of environmental pathogens and high cost preclude its regular use. Direct susceptibility testing based on Matrix Assisted Laser Desorption Ionization-Time of Fight (MALDI-TOF) enable early detection of resistant bacteria from sterile body fluid cultures and blood cultures.

28.8 Newer Markers

Newer biomarkers for detection of sepsis target the basic pathophysiological mechanisms. Markers of bacterial translocation such as calprotectin, endotoxin, D-lactate, and bacterial DNA are elevated. Other markers include lipopolysaccharide binding protein and mid region-proadrenomedullin. The evidence for these markers is based on small studies; further research is needed before it can be incorporated into clinical practice.

28.9 Approach to Patient

28.9.1 Management

The management principles for sepsis in cirrhotic patients do not differ from patients without cirrhosis. However, it presents its own unique set of challenges. Source localization and resuscitation should go hand in hand. Blood cultures, ascitic fluid counts and cultures, urine routine microscopic analysis, chest radiographs, and serum lactate levels should be done immediately. Prognostic scores, as mentioned above, should be calculated and dynamically assessed.

Cirrhosis is a state of hyperdynamic circulation; patients usually have a low-normal mean arterial pressure, and a higher heart rate. These patients may have lower hematocrit and underlying cardiac diastolic dysfunction. Targeting fluid strategies based on mean arterial pressure and central venous pressure may, therefore, be fallacious, and further studies are required before specific recommendations can be made. Administration of normal saline may worsen ascites, pedal edema and may lead to abdominal compartment syndrome. Another problem often encountered in patients with cirrhosis and sepsis is the presence of renal dysfunction. This just compounds the problem at hand, whereby an adequate amount of fluid needed, type of fluid needed, and the hemodynamic targets to be achieved all become difficult to establish. The choice, at best, is then based on strict monitoring of the hemodynamic parameters and responsiveness to the therapy.

28.9.2 Antibiotic Therapy

The surviving sepsis guidelines emphasize the importance of early initiation of antibiotic therapy in sepsis. Each hour of delay in giving antibiotics has been found to be associated with a decrease in survival of 7.6%. The often-debatable conundrum is the choice of the drug(s), and whether monotherapy is superior to combination therapy. The choice should be based on the local epidemiological data and the antibiotic resistance patterns. It should also be based on the probable focus of infection, the severity of infection, and whether the infection was community acquired or healthcare associated. History of antibiotic use for prophylaxis or treatment, use of corticosteroids and immunosuppressive drugs, and risk factors for invasive fungal infections must be taken into consideration before choosing the empirical antibiotic therapy. The culprit organism is identified in 20–50% of patients only. The antibiotics need to be changed or stopped based on sensitivity patterns, to prevent the emergence of antibiotic resistance. The duration of antibiotic therapy, again, remains a matter of preference in the absence of well-planned studies addressing the issue, except in patients with spontaneous bacterial peritonitis. The common infections and the drugs of preference are mentioned below.

Infection	Definitions
Community-acquired infections	Diagnosed within 48 h of admission without hospitalization in the previous 6 months and no recent contact with the healthcare system
Hospital-acquired infections (nosocomial infections)	Diagnosed after 48 h of admission

Choice of Antibiotics for different (sites) Infections in Cirrhosis

1. Community-acquired
   (a) third generation cephalosporin—Cefotaxime
   (b) Alternative—Piperacillin/Tazobactam, Cefoperazone/Sulbactam
   (c) Choice of antibiotics also depends upon previous culture reports, the site of infection and prior antibiotics received
2. Nosocomial infections
   (a) Carbapenem ± other antibiotics
   (b) Suspected organism and culture sensitivity patterns (vary from individual center to center)
   (c) Change antibiotics as per the culture reports
   (d) The antibiotic choice also depends upon the culture sensitivity pattern of the organisms according to the institution where the patient is admitted

28.9.3 Intravenous Albumin

Administration of human albumin is associated with improvement in the outcomes of several specific complications of cirrhosis. Among patients with cirrhosis and spontaneous bacterial peritonitis (SBP), particularly those with serum bilirubin level ≥ 4 mg/dL or those with serum creatinine ≥1 mg/dL, administration of human

albumin is associated with a reduction in the incidence of type 1 hepatorenal syndrome (HRS) and mortality. The role of albumin in infections other than SBP is not well defined. The mechanisms of the beneficial effects of human albumin include plasma volume expansion and its anti-oxidant and anti-inflammatory properties.

28.9.4 Nutrition

The basic principles of nutritional management in patients with chronic liver disease are similar to any other critical illness. Nutritional deficiencies should be assessed at the time of admission to the ICU. Enteral nutrition should be started as early as possible, in the absence of contra-indications. The optimal energy requirement is 25–35 kcal/kg/day, and the protein requirement is 1.2–1.5 g/kg/day. The calculations should be based on dry weight. The calories should be gradually increased to achieve more than 80% of the estimated targets over 24–48 h, and monitor for refeeding syndrome in severely malnourished patients. Patients on mechanical ventilation should receive feeds through the nasogastric tube. Appropriate measures such as elevation of the head end, use of prokinetics, and slow continuous infusion must be taken to prevent aspiration.

Patients with cirrhosis often have micronutrient deficiencies. Both fat and water-soluble vitamins and micronutrient deficiencies are often seen due to impaired hepatic reserve, hepatic dysfunction, inadequate intake, malabsorption, and alcohol consumption. It is vital that these deficiencies be corrected, even when clinical manifestations are not apparent. Vitamin D should be supplemented if levels are below 20 ng/mL. Thiamine should be supplemented in patients with alcohol-related cirrhosis. Deficiencies of other vitamins (folate, pyridoxine, and cobalamin) and trace elements (iron, zinc, and calcium) must be corrected.

28.10 Organ Support

Renal replacement support, respiratory (ventilator) support needs to be provided to patients as required. The use of invasive catheters is associated with an increased risk of infections. Till date, none of the liver support systems—e.g. Molecular Adsorbent Recirculating System (MARS)—has shown added benefit in improving the outcome in patients with cirrhosis. The present-day role of high volume plasma exchange is unclear among patients with cirrhosis with the available literature.

28.11 Management of Associated Complications

It is essential to manage associated complications like gastrointestinal bleeding with endoscopic therapies, as required. Correction of deranged coagulation parameters—like low platelet count and prolonged international normalized ratio (INR)—is not recommended in the absence of active bleeding. Thromboelastography, which is a

point of care test and assesses the global coagulation cascade, is useful for guiding blood product transfusions in these patients. Correction of dyselectrolytemia—hyponatremia, hypernatremia, hypokalemia, hyperkalemia, hypoglycemia—and supplementation of trace elements should be done as required. Blood sugars need to be controlled with insulin among patients with diabetes. Among patients with altered sensorium, it is essential to rule out intracranial bleed with a CT head. Management of hepatic encephalopathy includes identification and management of precipitating events and drugs such as lactulose (30–60 ml TDS till 2–3 semi-solid stools), rifaximin, and L-Ornithine L-Aspartate. Alcohol intoxication and withdrawal need to be managed, as appropriate. Underlying etiologies of liver disease (hepatitis B virus, autoimmune liver hepatitis, Wilson's disease) need to be treated, along with the management of sepsis.

28.12 Liver Transplantation

Liver transplantation is the definitive treatment in decompensated cirrhosis. Presence of active infection is a contraindication for liver transplant. Patients can be considered for liver transplant after control of sepsis.

28.13 New Research/Novel Therapy

Management strategies which can target the prevention of development of infection need to be explored. Potential targets include prevention of bacterial translocation across the intestinal barrier, boosting the host immune response to control infection. Also, inappropriate use of antibiotics should be stopped to prevent anti-microbial resistance. Newer techniques (point of care) which can help in detecting infection early and assessing the sensitivity pattern of various microorganisms can help in reducing cost and improving the outcome. Ammonia plays an essential role in the pathogenesis of hepatic encephalopathy in cirrhosis patients. Ammonia is associated with neutrophil dysfunction, which in turn predisposes to infections. Future studies are needed to explore the effect of ammonia reduction and infection. Also, therapies for liver regeneration need to be explored among cirrhosis patients with sepsis.

Further Reading

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