GUIDELINES

Guidelines for Antibiotics Prescription in Critically Ill Patients

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Executive Summary

Pharmacokinetics and Pharmacodynamics

Evidence Statement

Time-dependent antibiotics require drug concentrations greater than the minimum inhibitory concentration (MIC) for a certain time period between doses, which usually ranges from 40 to 50% of inter-dose interval for their best action. Continuous infusions are preferred over extended infusions for beta-lactam antibiotics and are associated with clinical benefits like decrease in hospital stay, cost of therapy and mortality. For vancomycin, continuous infusion is associated with reduced toxicity and cost of therapy but no mortality benefit.

Newer Diagnostics Including Multiplex PCR

Recent times have seen a surge in rapid culture-independent novel assays and molecular diagnostics for common respiratory pathogens, as well as the availability of updated tests for newer strains of pathogens. These include antigen detection assays, reverse transcription–quantitative polymerase chain reaction (RT-qPCR) testing, multiplex PCR panels targeting multiple organisms, plasma cell-free DNA, next-generation sequencing (NGS), etc. on blood, and upper and lower respiratory tract specimens to detect viral, bacterial, fungal, and *mycobacteria*l infections. Appropriate use of these newer methods leads to reduced antibiotic usage.

Community-acquired *Pneumoniae* in the Intensive Care Unit

What are the Common Organisms Causing Community-acquired *Pneumoniae* in Intensive Care Unit Worldwide and in India?

Evidence Statement

Viruses (including influenza), *Streptococcus pneumoniaee*, gram-negative bacilli (including *klebsiella*), *Haemophilus influenzae* and atypical organisms (*Mycoplasma pneumoniaee*) and are common causes of community-acquired *pneumoniae* (CAP) in intensive care unit (ICU). *Staphylococcus aureus*, *Legionella* and *Mycobacterium tuberculosis* are less common causes of CAP in ICU. *Pseudomonas aeruginosa* is an important pathogen causing CAP in patients with structural lung disease. Methicillin-resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant

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gram-negative organisms are relatively infrequent causes of CAP in India and are associated with risk factors such as structural lung disease and previous antimicrobial intake. Anaerobic organisms may cause CAP or co-infection in patients with risk factors for aspiration like elderly, altered sensorium, dysphagia, head and neck malignancy. *S. pneumoniae*e remains sensitive to beta-lactams and macrolides. *Haemophilus influenzae* has good sensitivity to beta-lactam with beta-lactamase inhibitors and fluoroquinolones. Recent studies show increasing prevalence of extended spectrum β-lactamase (ESBL) producing *enterobacter*iaceae. Newer agents like omadacycline, delafloxacin and Lefamulin have added advantages of being effective against MRSA and anaerobes. Omadacycline and delafloxacin are effective against GNBs, whereas only Delafloxacin has good sensitivity against *pseudomonas*. Nafcillin and oxacillin are preferred agents for MSSA whereas agents effective against MRSA *pneumoniae* include linezolid, vancomycin and teicoplanin.

What are the Risk Factors for Multidrug-resistant (MDR) Pathogens for CAP in ICU?

Evidence Statement

Risk factors for multidrug-resistant (MDR) organisms include age > 65 years, antimicrobial therapy in the preceding 3 months, high frequency of antibiotic resistance in the community, hospitalization for ≥48 h in the preceding 3 months, home infusion therapy including antibiotics, home wound care, chronic dialysis within 1 month, family member with MDR pathogen and ongoing immunosuppressive treatment.

Recommendation

- All patients admitted with CAP in ICU should be evaluated for risk factors for infection with MDR organisms (2A).
- Antibiotic therapy should be individualized to cover the commonly implicated organisms according to risk factors, including *Pseudomonas*, ESBL producing *enterobacter*iaceae or MRSA (3A).
- If antipseudomonal, MRSA specific or non-standard antibiotics are initiated emperically, early microbiologic diagnosis of respiratory secretions (Gram stain, PCR or multiplex PCR) and blood cultures should be sought for early de-escalation or narrowing down antimicrobial therapy (3A).

Should Serum Procalcitonin Levels be Done at Baseline in Patients Admitted with CAP in ICU?

Evidence Statement

Serum procalcitonin has moderate sensitivity and specificity in differentiating bacterial and viral etiology in CAP. Serial measurements of procalcitonin are useful in limiting antibiotic exposure in ICU patients with lower respiratory tract infections, predominantly by early cessation.

Recommendation

- Serum Procalcitonin should not be used to differentiate bacterial and viral etiology in CAP in ICU (1A).
- Serum procalcitonin levels should be measured at baseline and serially for use in antibiotic de-escalation for CAP in ICU (1A).

How Early should the Antibiotics be Initiated in Patients with CAP Who Require ICU Admission?

Evidence Statement

Early initiation of antibiotics has been associated with reduction in all-cause mortality in community-acquired *pneumoniae*, including severe *pneumoniae* with sepsis or septic shock.

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Recommendation

- Appropriate antimicrobial therapy should be initiated as early as possible in patients of CAP requiring ICU admission, preferably within the first hour after obtaining necessary microbiologic samples (3A).
- Respiratory samples should be sent for Gram stain, bacterial culture, and other investigations as clinically indicated, as early as possible (3A).
- Multiplex PCR may be used to obtain precise microbiologic diagnosis in patients with CAP admitted to ICU if feasible (2B).

Should CAP in ICU Receive Empirical Antimicrobials or Upfront Targeted Antimicrobial Therapy?

Evidence Statement

Early institution of targeted antibiotic therapy in severe CAP based on urinary antigen testing is associated with higher relapse rate without any mortality benefit in prospective randomized studies. Retrospective studies have shown mortality benefit with narrowing down of antibiotic therapy based on results from cultures of respiratory specimens, blood cultures as well as *Legionella* and pneumococcal urinary antigen testing. Multiplex PCR based diagnostic testing of respiratory specimens leads to more appropriate and focused antimicrobial therapy administration.

Recommendations

- Empirical therapy covering common etiologic organisms should be initiated for severe CAP requiring ICU admission (2A).
- Investigations including culture of respiratory secretions (sputum, endotracheal aspirate), blood cultures, urinary antigen testing for pneumococcus and *Legionella* may be performed to narrow down therapy. (UPP)
- Multiplex polymerase chain reaction (PCR) testing of respiratory specimens, if available, should be performed for CAP in ICU for microbiologic diagnosis and subsequent antibiotic modification or de-escalation (3A).
- PCR testing for viral etiology (e.g., influenza, SARS-Cov2) should be performed based on seasonality and local guidelines (3A).
- Bronchoscopic BAL or protected specimen brush samples may be performed for microbiologic diagnosis on case by case basis (3A).

What is the Current Role of Radiologic Investigations in Guiding Antibiotic Therapy for CAP in ICU?

Evidence Statement

Lung ultrasound has high sensitivity and specificity in diagnosis of *pneumoniae*, and better diagnostic accuracy as compared to chest X ray. Addition of lung ultrasound aids in improving confidence in diagnosis of CAP and leads to significant treatment modification. CT Chest leads to early diagnosis of CAP in ICU and modification of treatment in significant proportion of cases, though there is insufficient evidence in impact on short term outcomes.

Recommendations

- Bedside chest ultrasound should be done for all suspected CAP patients in ICU at baseline, and at frequent intervals as indicated (1A).
- CT Chest may be done for diagnosis of CAP in ICU in cases where diagnosis is in doubt, alternate causes (heart failure, pulmonary embolism) are suspected, to rule out rarer causes (e.g., tuberculosis, *nocardia*) or to decide on site of invasive sampling (bronchoscopy or image guided sampling) (3A).

For Empirical Therapy in Patients with CAP in ICU, Should Combination Therapy be Preferred Over Monotherapy?

Evidence Statement

Empirical combination therapy covering common organisms causing community-acquired *pneumoniae* improves survival without any significant increase in microbial resistance.

Recommendation

- Patients with CAP requiring ICU admission should initially receive combination of empirical antimicrobial agents covering common causative organisms (2A).

What should be the Preferred Combination Therapy for CAP in ICU?

Evidence Statement

For patients with severe CAP requiring ICU admission without risk factors for pseudomonal infection, a combination of beta-lactams along with macrolides is better as compared to beta-lactam fluoroquinolone combination in terms of mortality benefit and length of hospital stay.

Recommendation

- For patients with CAP requiring ICU admission, a non-pseudomonal beta-lactam (cefotaxime, ceftriaxone, or amoxicillin–clavulanic acid) plus a macrolide (azithromycin or clarithromycin) should be preferred if there are no risk factors for *Pseudomonas aeruginosa* infection (1A).
- For penicillin-allergic patients, a respiratory fluoroquinolone (levofloxacin, moxifloxacin or ciprofloxacin) and aztreonam may be used (3A).
- If macrolides cannot be used, a fluoroquinolone may be used if there is no clinical suspicion of tuberculosis, after sending sputum or endotracheal aspirate for AFB and Genexpert (3A).

When should Anti-pseudomonal Cover be Added for CAP in ICU? If Required, which are the Preferred Antimicrobials for Anti-pseudomonal Cover?

Evidence Statement

For patients with severe CAP requiring ICU admission, risk factors for infection with *Pseudomonas aeruginosa* include chronic pulmonary disease (chronic obstructive pulmonary disease, asthma, bronchiectasis), frequent systemic corticosteroid use, prior antibiotic therapy, old age, immunocompromised states, enteral tube feeding, cerebrovascular or cardiovascular disease. Prior antibiotic therapy is a risk factor for multidrug-resistant pseudomonal infection.

Recommendation

- If *P. aeruginosa* is an etiological consideration, antipneumococcal, antipseudomonal antibiotic (like ceftazidime, cefoperazone, piperacillin–tazobactam, cefoperazone–sulbactam, imipenem, meropenem or cefepime) should be used (2A).
- Combination therapy should be considered with addition of aminoglycosides or antipseudomonal fluoroquinolones (e.g., ciprofloxacin) (3A).
- If empiric antipseudomonal treatment is started, a culture of respiratory specimens (sputum, miniBAL or BAL) should be obtained to confirm pseudomonal infection or subsequent de-escalation (3A).

When should MRSA Cover be Added to Empiric Regimen for CAP in ICU?

Evidence Statement

Risk factors for MRSA in CAP in ICU include close contact with MRSA carrier or patient, influenza, prisoners, professional athletes, army recruits, men having sex with men (MSM), intravenous (IV) drug abusers, regular sauna users and those with recent antibiotic use. MRSA *pneumoniae* should be suspected after influenza or in previously healthy young patients, if there is cavitation or necrotizing *pneumoniae*, along with rapid increase of pleural effusion, massive hemoptysis, neutropenia or erythematous rashes. Vancomycin, teicoplanin, linezolid and tigecycline are effective antibiotics against MRSA.

Recommendation

- All patients admitted with CAP in ICU should be evaluated for presence of risk factors associated with MRSA (3A).
- If MRSA is a consideration, empiric linezolid (1A), vancomycin (1A) or teicoplanin (2A) should be added to the regimen. Linezolid should be used for vancomycin intolerant patients, vancomycin-resistant *Staphylococcus aureus* (VRSA), or patients with renal failure (1A).
- PCR and Gram stain of nasal swab, along with Gram stain and culture of respiratory specimens should be obtained for microbiologic diagnosis of MRSA if empiric MRSA treatment is initiated, for future de-escalation or targeted antimicrobial therapy (3A).

When should Anaerobic Cover be Added to Empiric Antibiotic Regimen for CAP in ICU?

Evidence Statement

Risk factors for aspiration *pneumoniae* in patients admitted with CAP in ICU include dysphagia, altered sensorium, coma, witnessed

aspiration, putrid discharge, presence of lung abscess, empyema, or necrotizing *pneumoniae*. There is no significant difference in anaerobic flora of CAP patients with or without aspiration. Severe aspiration related CAP has increased prevalence of GNBs and decreased prevalence of GPCs.

Recommendation

- Empirical antibiotics with anaerobic coverage should be considered for treatment of CAP in ICU in presence of witnessed aspiration, lung abscess, empyema, or necrotizing *pneumoniae* (2A).
- Specific antibiotics with anaerobic coverage (such as clindamycin and metronidazole) should not be routinely prescribed in severe CAP (UPP).

Which Antibiotic should be Preferred for Anaerobic Coverage for CAP in ICU?

Evidence Statement

Commonly prescribed empirical antibiotics for CAP in ICU such as ampicillin-sulbactam, amoxicillin-clavulanic acid, piperacillin-tazobactam and carbapenems have excellent anaerobic coverage. Clindamycin and moxifloxacin are effective against aspiration *pneumoniae* and lung abscess caused by anaerobic organisms. Lung abscess and necrotizing *pneumoniae* may require prolonged treatment up to 4 to 6 weeks.

Recommendation

- Patients with CAP due to anaerobic infection should be initiated on antibiotics with anaerobic activity such as amoxicillin-clavulanate, clindamycin or moxifloxacin (1A).
- Piperacillin-tazobactam or carbapenems can be used for empirical therapy in CAP due to anaerobes if otherwise indicated (3A).
- Duration of treatment should be individualized according to response and severity of disease (3A).

What should be the Optimal Duration of Antibiotics for CAP in ICU?

Evidence Statement

For CAP in ICU, there is limited evidence regarding duration of treatment, with no significant mortality benefit beyond 7 days of antimicrobial therapy in uncomplicated cases. However, CAP due to GNB, *enterobacter*iaceae, *P. aeruginosa*, *S. aureus* bacteremia and *L. pneumophila* requires prolonged treatment. Necrotizing *pneumoniae*, lung abscess, empyema or extrapulmonary infective complications like meningitis or infective endocarditis also require longer duration of treatment.

Recommendation

- Patients with CAP requiring ICU admission should receive antibiotics for 7 to 10 days (2A).
- Patients with CAP due to *Pseudomonas* or aspiration *pneumoniae* should be treated for 14 days (3A).
- Necrotizing *pneumoniae* due to GNB, MRSA or anaerobes also require treatment for 14 to 21 days (3A).
- Duration of treatment should be individualized according to causative organism, response, severity of disease and complications (3A).

What is the Role of Adjunctive Therapy, i.e., Systemic Corticosteroids and Inhaled Antibiotics for CAP in ICU?

Evidence Statement

Short course of systemic corticosteroids has been associated with reduced risk of mortality, need for endotracheal intubation and inotrope initiation in severe CAP. Systemic corticosteroids are associated with reduced need for ICU admission and endotracheal intubation in patients hospitalized with CAP, albeit with higher risk of readmission rates. However, large trials have excluded patients with septic shock, pregnancy, immunodeficiency, viral infections (influenza, herpes, acute viral hepatitis), tuberculosis and invasive fungal infections. Hydrocortisone 200 mg to 240 mg daily infusion was most commonly used regimen in CAP trials for 7 to 10 days.

The evidence for inhaled antibiotics is predominantly from hospital-acquired and ventilator-associated *pneumoniae*, with better odds of clinical cure and microbiologic eradication in adjunct inhaled antibiotic therapy.

Recommendation

- Short courses of systemic steroids should be given for patients with severe CAP after careful risk-benefit analysis (1A).
- Hydrocortisone 200 mg infusion over 24 hours for 5 to 7 days should be used for systemic corticosteroid administration in severe CAP patients (2A).
- Inhaled antibiotics may be used in severe CAP patients on a case-to-case basis. (UPP)

Should Procalcitonin be Used to Determine Duration of Antibiotic Administration for CAP in ICU?

Evidence Statement

Serial procalcitonin levels can be used to de-escalate antibiotics for CAP in the ICU without increasing mortality or recurrence rates.

Recommendation

- Procalcitonin levels can be used along with clinical judgement for de-escalation of antibiotics in CAP in ICU in patients treated beyond 5-7 days (1A).

Hospital-acquired *Pneumoniae* and Ventilator-associated *Pneumoniae*

What are the Common Organisms Causing HAP/VAP in ICU and What is their Antibiotic Susceptibility Pattern?

Evidence Statement

Ventilator-associated *pneumoniae* (VAP) and hospital-acquired *pneumoniae* (HAP) are commonly caused by aerobic gram-negative bacilli, such as *Acinetobacter baumannii, klebsiella pneumoniaee, Pseudomonas aeruginosa,* or by gram-positive cocci (*Staphylococcus aureus*). In Indian ICUs, gram-negative organisms are most common etiologic agents (i.e., *Acinetobacter, Klebsiella and Pseudomonas* spp). Most of these pathogens have been found to be multidrug-resistant. Frequency of specific MDR pathogens causing HAP and VAP may vary by hospital, patient population, type of ICU patient, and change over time. Pan resistant organisms are increasingly being reported. Invasive sampling (including bronchoalveolar lavage) leads to better microbiologic diagnosis in HAP and VAP, but has not been associated with improved outcomes.

Should Baseline Serum Procalcitonin be Measured in Patients with Suspected VAP?

Evidence Statement

Baseline serum procalcitonin has moderate sensitivity and specificity for the diagnosis of ventilator and hospital-acquired *pneumoniae*, and cannot reliably differentiate between ventilator-associated tracheobronchitis and ventilator-associated *pneumoniae*. An 80% decline from baseline procalcitonin levels has been used along with absolute value of less than 0.5 mL to make decisions regarding antibiotic de-escalation.

Recommendation

- Serum procalcitonin should not be used for diagnosis of Ventilator-associated or Hospital-acquired *Pneumoniae* or for decision making regarding antibiotic initiation (1A).
- Baseline procalcitonin levels may be measured in VAP, for future use in antibiotic de-escalation (2B).

What are the Risk Factors for MDR Pathogens in VAP in ICU?

Evidence Statement

The risk factors for VAP due to MDR organisms include age >60 years, duration of mechanical ventilation ≥7 days, prior antibiotic use within 3 months, presence of severe sepsis or septic shock at time of VAP, ARDS preceding VAP, renal replacement therapy prior to VAP, systemic corticosteroid therapy and high prevalence (>25%) of MDR organisms in the hospital setting.

What should be the Initial Combination of Empiric Antibiotic Therapy for VAP in ICU?

Evidence Statement

Use of combination therapy for VAP has better outcomes in patients who are at risk for MDR pathogens. Commonly used antimicrobial agents include piperacillin-tazobactam, cefepime, levofloxacin, imipenem and meropenem. Among antimicrobial agents, carbapenems have a higher chance of clinical cure than non-carbapenems. Patients with high risk of MDR HAP or VAP, i.e., those admitted in ICUs with high prevalence of MDR organisms, prior isolation of MDR GNBs from respiratory secretions have been treated with combination therapy of carbapenems or beta-lactams with colistin or polymyxin. Monotherapy with newer beta-lactam-beta-lactamase combinations (e.g., ceftazidime-avibactam) or carbapenem-beta-lactamase combination (e.g., Imipenem-cilastatin-relebactam, meropenem-vaborbactam) have better outcomes and less toxicity as compared to other available regimens or polymyxins. Polymyxin B and colistin have been found to be efficacious in treatment of carbapenem resistant *Klebsiella* and *Acinetobacter*, but colistin has a higher incidence of nephrotoxicity. Tigecycline and minocycline are alternative options for CRE infections when *pseudomonas* is not a consideration. Aztreonam as a part of combination therapy is an alternative when newer beta-lactam-beta lactamase combinations are not available, or in presence of metalloproteinases like NDM. For treatment of VAP due to MRSA, glycopeptides and linezolid have similar clinical success, however, linezolid may be associated with higher chance of thrombocytopenia and gastrointestinal adverse events. Adjunct nebulized antibiotics (colistin, aminoglycosides) have been found to increase microbiologic eradication without any mortality benefit in VAP and HAP.

Gram staining of respiratory secretions can lead to lesser prescription of anti-pseudomonal and anti-MRSA antibiotics without compromising clinical cure rates in ICUs with low MDR organism prevalence. Molecular techniques like multiplex PCR have a very less turnaround time and can be used to effectively modify empiric regimen for HAP and VAP.

Recommendation

- Among patients with VAP who are at high risk of MDR pathogens or are in ICU with high prevalence of MRSA (>15%) and resistant gram-negative organisms (>10%), an agent active against MRSA and at least two agents active against gram-negative organisms including *P. aeruginosa* is recommended (3A).
- Among patients with VAP who are not at high risk of MDR pathogens and are in ICU with high prevalence of resistant gram-negative organisms (>15%) but low prevalence of MRSA (<10%), two agents active against gram-negative organism including *P. aeruginosa* is recommended (3A).
- Linezolid, vancomycin or teicoplanin should be used for empiric MRSA coverage in patients at high risk of MRSA (1A).
- In patients with high risk for MDR GNBs and prior isolation of MDR or carbapenem resistant GNBs from respiratory secretions, monotherapy with newer agents (Ceftazidime-avibactam, Ceftolozane-tazobactam, Imipenem-cilastatin-relebactam or Meropenem-vaborbactam) should be preferred to combination therapy (2A).
- Polymyxin B (preferred) or colistin as part of empiric combination regimen can be used in the ICUs with high prevalence of carbapenem-resistant *enterobacter*iaceae (>20%) in patients with risk factors for MDR or XDR gram-negative pathogens (2A).
- In patients with high risk for MDR GNBs or prior isolation of MDR/carbapenem resistant GNBs from respiratory secretions, tetracyclines (tigecycline or minocycline) may be used as part of combination therapy if no alternate drugs can be given, in patients without bacteremia, and *pseudomonas* is not a consideration (3B).
- In patients with high risk for MDR GNBs, aztreonam can be used as part of combination regimen if no alternate drugs are available or pseudomonal coverage is needed (3A).
- In ICU where distribution of pathogen and antibiotic resistance pattern is known, empiric treatment should be designed accordingly, based upon patient risk factors for MDR pathogens (UPP).
- Adjunct nebulized antibiotics (colistin, aminoglycosides) can be used in combination with systemic therapy for empiric treatment of VAP on case-to-case basis or microbiologic sensitivity (3A).
- Invasive sampling (Nonbronchoscopic BAL or bronchoscopic BAL, protected specimen brushing) should be performed in VAP for microbiologic diagnosis and definitive antibiotic therapy (2A).
- Multiplex PCR of respiratory specimens (non-bronchoscopic BAL, or bronchoscopic BAL) should be used for early identification of causative organisms and appropriate modification of antibiotic therapy (2A).
- Gram stain of respiratory specimens can be used for early de-escalation of empiric anti-MRSA therapy (2A).
- In our country or in areas with high endemicity of tuberculosis, use of linezolid may be restricted unless no suitable alternative is available (UPP).
- Fluoroquinolones and aminoglycosides should be cautiously used as monotherapy in VAP in our country as well as in other areas with high endemicity of tuberculosis. (UPP)

When to Give Antipseudomonal Drugs for VAP in ICU?

Evidence Statement

Prior use of antibiotics (most consistent association), prolonged duration of mechanical ventilation, and chronic obstructive pulmonary disease (COPD) have been identified as risk factors for MDR *P. aeruginosa* infection.

Recommendation

- Empiric treatment should be given to cover *Pseudomonas* if there are risk factors for MDR *Pseudomonas* infection (2A).
- In ICUs where gram-negative isolate resistance rate is high (>10 % gram-negative isolate resistant to agent being considered for monotherapy or not known), two anti-pseudomonal antibiotics from different class to be given (3A).

What should be the Duration of Antibiotic Treatment for HAP/VAP?

Evidence Statement

Short-course regimens for VAP are associated with significantly more antibiotic-free days without any significant difference in duration of ICU or hospital stay, recurrence of VAP and mortality. Short-course regimens are associated with more recurrences in VAP due to non-fermenting gram-negative bacilli (NF-GNB).

Recommendation

- Short course (7-8 days) of antibiotic therapy should be used, in case of VAP with good clinical response to therapy (1A).
- Longer duration (14 days) of antibiotic therapy should be considered, in case of VAP caused by NF-GNBs or is associated with severe immunodeficiency, structural lung disease (COPD, bronchiectasis, and interstitial lung disease), empyema, lung abscess, necrotizing *pneumoniae* and inappropriate initial antimicrobial therapy (3A).

When should Anaerobic Cover be Added for VAP and Which is the Preferred Antimicrobial Agent?

Evidence Statement

Incidence of anaerobic bacteria as causative agent of VAP is 2 to 7%. Risk factors for VAP due to anaerobes are altered consciousness, aspiration pneumonitis and high simplified acute physiology score (SAPS).

Recommendation

- Empirical antibiotic regimen for VAP should not include coverage for anaerobic organisms routinely (2A).
- In the presence of risk factors for VAP due to anaerobic pathogens, anaerobic antimicrobial coverage should be added in empirical regimen (2B).
- In patients with risk factors for anaerobic organisms, clindamycin or metronidazole should be added to empirical antibiotics regimen for VAP, if it does not include carbapenems (meropenem or imipenem) or piperacillin-tazobactam in the ongoing empirical regimen (UPP).

When to Give Atypical Cover for VAP and Which is the Preferred Agent?

Evidence Statement

Incidence of a typical bacteria as causative agents of VAP is low (5 to 7.5%). Risk factors for VAP due to *Legionella* are *Legionella* colonization in hospital water supply, prolonged use of corticosteroids, cytotoxic chemotherapy, elderly, chronic renal failure, previous antibiotic use, granulocytopenia and poor Glasgow coma score.

Recommendation

- Empirical antibiotic regimen for VAP should not include coverage for atypical organisms routinely (2A).
- In the presence of risk factors for VAP due to atypical bacterial pathogens, atypical antimicrobial coverage should be added to empirical regimen (2B).
- The preferred atypical coverage in combination antibiotics regimen is fluoroquinolones (levofloxacin or moxifloxacin) or macrolides (azithromycin or clarithromycin) (UPP).

Can Serum Procalcitonin be Used for De-escalation of Antibiotic Therapy in VAP?

Evidence Statement

Use of procalcitonin to guide de-escalation of antibiotic treatment in patients with VAP is effective in reducing antibiotic exposure, without an increase in the risk of mortality or treatment failure.

Recommendation

- Serum procalcitonin may be used to guide the de-escalation of antibiotics in VAP, when the anticipated duration of therapy is >7–8 days (1B).
- Serum procalcitonin levels (together with clinical response) should be used for de-escalation of antibiotic therapy in VAP in specific clinical conditions (severely immunocompromised patients, drug resistant pathogens-NF-GNB, initial inappropriate therapy) (3A).

How to Approach a Patient of Non-responding VAP?

Evidence Statement

Re-evaluation at 48 to 72 hours after the initial diagnosis of VAP is the most suitable time. By then the results of the initial microbial investigation are usually available and treatment modification can be done. Evaluation of treatment response for VAP should be on the basis of clinical, laboratory, radiograph and microbiological results. Factors associated with treatment failure in VAP includes host factors (advanced age, immunosuppressed, chronic lung disease, ventilator dependence), bacterial factors (drug resistant pathogens, opportunistic pathogens), therapeutic factors (inappropriate antibiotics, delayed initiation of therapy, insufficient duration of therapy, suboptimal dosing, inadequate local concentration of drugs), complications of initial VAP episode (lung abscess, empyema), other non-pulmonary infections or non-infectious mimics of *pneumoniae*.

Recommendation

- Non-responding VAP should be evaluated for non-infectious mimics of *pneumoniae*, unsuspected or drug-resistant pathogens, extrapulmonary sites of infection, and complications of *pneumoniae* or its therapy and diagnostic testing should be directed to whichever of these causes is likely (2A).
- CT Chest and other indicated imaging modalities should be performed to clarify diagnosis in non-responding VAP and HAP (3A).
- Microbiologic analysis of blood, respiratory specimen (non-bronchoscopic or bronchoscopic BAL) and other samples like pleural fluid should be performed using conventional culture and molecular methods for identification of pathogens in non-responding HAP and VAP (3A).

Catheter-related Bloodstream Infections (CRBSI)

What is the Incidence of Catheter Colonization and CRBSI?

Evidence Statement

The global incidence of CC ranges from 1.4 % to 19.4 % whereas CRBSI incidence ranges from 2.4 % to 12.5 %. The incidence of CC is higher in Indian ICUs ranging from 18 % to as high as 59 %, whereas incidence of CRBSI is up to 16.1 per 1000 catheter days.

What are the Risk Factors for CRBSI?

Evidence Statement

Longer indwelling catheter duration, immunosuppression, diabetes mellitus, sepsis at the time of insertion, multilumen catheters and APACHE >23 are important risk factors for CRBSI. APACHE at admission, renal failure, central venous catheterization and steroid therapy are important risk factors for fungal CRBSI.

What are the Common Organisms Causing CRBSI and their Antibiotic Susceptibility?

Evidence Statement

Coagulase-negative staphylococci (CONS), *S. aureus*, enterococcus and *Candida* species are the common organisms accounting for majority of the CRBSIs. Large proportion of *Staphylococcus aureus* and CONS are methicillin resistant ranging from 11 % to 87 %. There is an increased incidence of CRBSI due to gram-negative organisms (most of which are ESBL producers) and *Candida* especially the non-albicans *Candida*.

What is/are the Empiric Antibiotic(s) of Choice for CRBSI in ICU?

Evidence Statement

Vancomycin, teicoplanin, linezolid and daptomycin are effective in treatment of CRBSI due to MRSA and MR-CONS. Fourth-generation cephalosporin, carbapenem or beta-lactam/beta-lactamase combination like piperacillin-tazobactam and aminoglycosides might be used for gram-negative organisms causing CRBSI. Caspofungin and fluconazole have been equally effective as amphotericin-B for treatment of candidemia. However, increasingly fluconazole resistant *Candida* are becoming more common, and echinocandins are preferred as initial therapy in suspected catheter-related bloodstream infections due to *Candida*.

Recommendation

- Empirical antibiotic regimen for CRBSI should include coverage for both gram-positive and gram-negative organisms. (2A)
- Vancomycin or teicoplanin is the recommended first line drug for the empiric treatment of CRBSI for MRSA and MR-CONS while linezolid and daptomycin are good alternative agents. (2A)
- Empiric coverage for gram-negative bacilli should include a fourth-generation cephalosporin, a carbapenem, or a β-lactam/β-lactamase inhibitor combination, newer agents (like ceftazidime-avibactam) or without an aminoglycoside. (UPP)
- An echinocandin should be used as empirical antifungal agent for treatment of suspected central line-associated candidemia. (2A)

What should be the Duration of Antibiotic Treatment for CRBSI?

Evidence Statement

Short duration (<14 days) of antibiotics is as effective as longer duration (>14 days) for uncomplicated *Staphylococcus aureus* bacteremia. Complicated bacteremia due to *S. aureus* or those associated with endocarditis should receive longer duration. For gram-negative bacteremia, seven days of antibiotics is sufficient. In responding patient with uncomplicated CONS infection, 5-7 days therapy is considered optimum. Minimum 14 days treatment with antifungals is required for fungal CRBSI.

Recommendation

- Minimum 2 weeks antibiotics should be given for uncomplicated and 4-6 weeks for complicated *Staphylococcus aureus* CRBSI and infective endocarditis (2A).
- Minimum 7 days of antibiotics should be given for gram-negative CRBSI (2A).
- Five to seven days antibiotics are recommended for CONS bacteremia (3A).
- For suspected fungal CRBSI, antifungal therapy for at least 14 days is recommended (UPP).

Empirical Antibiotics for Urinary and Urogenital Sepsis in ICU

What is the Incidence of UTI in I Evidence Statement ICU? What are the Common Organisms and Risk Factors for UTI in ICU?

Evidence Statement

Incidence of CA-UTI ranges from 5-30% of all ICU admissions. The most common organism causing UTI in ICU are gram-negative bacteria (*E. coli, Klebsiella*) and fungi (especially *Candida*). Risk factors for UTI in ICU include duration of catheterization, length of ICU stay, prior antibiotic use, higher disease severity score, and female gender.

What is the Empirical Antimicrobial Agent of Choice for Treating UTI in ICU?

Evidence Statement

There has been a trend towards increasing prevalence of extended spectrum beta-lactamase producing gram-negative bacteria in the urinary cultures of catheter associated UTI. Aminoglycosides, beta-lactams along with a beta-lactamase inhibitor as well as carbapenems and fosfomycin have good efficacy in catheter associated UTI. The susceptibility for fluoroquinolones is decreasing over time among organisms isolated from nosocomial UTI. *Candida* species isolated from the patients with UTI show sensitivity to fluconazole, but increasingly fluconazole resistance is being reported.

Recommendations

- Initial choice of antibiotics should cover for ESBL producing gram-negative organisms and includes aminoglycosides, beta-lactam along with a beta-lactamase inhibitor or carbapenems (2A).
- In initial empirical regimen for UTI, antibiotics against gram-positive organisms is not recommended (3A).
- In appropriate clinical settings antifungals should be considered in the empirical regimen. Fluconazole is preferred, amphotericin

deoxycholate is an alternative if fluconazole resistance is suspected (3B).
- Catheter removal, if no longer indicated, or intermittent catheterization should be done in patients with catheter associated urinary tract infection (3A).

Acute Infective Diarrhea, Antibiotic-induced Diarrhea, and *Clostridium difficile*-associated Diarrhea in the ICU

What are the Common Organisms Causing Acute Infective Diarrhea in the ICU?

Evidence Statement

The incidence of diarrhea in the ICU ranges from 12.9 to 38%. Majority of the cases of diarrhea in ICU are non-infectious in etiology. *Clostridium difficile* is responsible for majority of infectious cases of diarrhea in ICU.

What are the Empirical Antibiotics of Choice for Treating Acute Infective Diarrhea in the ICU?

Evidence Statement

Empirical use of metronidazole in patients with diarrhea suspected due to *Clostridium difficile* in ICU setting results in significant symptomatic improvement.

Recommendation

- We recommend that empiric metronidazole be used for therapy of patients with acute diarrhea in the ICU with suspected *Clostridium difficile* infection (3A).

What are the Risk Factors for the Development of CDI or CDAD?

Evidence Statement

Risk factors for development of CDI include prior antibiotic therapy, advanced age, prolonged ICU/hospital stay, immunosuppression, proton pump inhibitors and enteral feeding. Cephalosporins, clindamycin, fluoroquinolones, carbapenems and penicillin derivatives are the commonly implicated antibiotics for CDAD/CDI.

What is the Recommended Treatment for CDI/CDAD: Which Antibiotics and Duration? Should Offending Antibiotics be Stopped? What is the Role of Probiotics in the Treatment of CDAD? How Should Recurrent *Clostridium difficile* Infection be Treated?

Evidence Statement

Both metronidazole and oral vancomycin have similar efficacy in clinical and bacteriologic cure of CDI. Use of implicated antibiotic after completing the treatment of CDI is associated with increased risk of recurrence of CDI. There is insufficient evidence to justify the use of probiotics as an adjunct to antibiotics in the treatment of CDAD. In a single RCT, fecal microbiota transplantation was found to be highly efficacious for treatment of recurrent CDI.

Recommendations

- We recommend metronidazole as the first line treatment of mild to moderate CDI/CDAD (1A).
- We recommend oral vancomycin as the first line treatment of microbiologically proven severe CDI/CDAD (1A).
- We recommend oral vancomycin as the treatment of recurrent CDI/CDAD infection (2A).
- We recommend fecal microbiota transplantation as an alternate treatment of recurrent CDI/CDAD infection (2A).
- We recommend that implicated antibiotics should be discontinued as soon as clinically feasible (2A).
- We recommend against the use of probiotics as an adjunct for the treatment of CDI/CDAD (2A).
- We recommend addition of vancomycin to a patient with microbiologically proven CDI/CDAD, if the patient is already on metronidazole or has no clinical response to metronidazole within 3-4 days (UPP).

Abdominal Infections in ICU Acute pancreatitis and Infected Pancreatic Necrosis

What is the Incidence, Risk Factors and Microbiology of Pancreatic Infection Following Acute Pancreatitis?

Evidence Statement

Incidence of pancreatic infection following acute pancreatitis ranges from 12-37%. Presence of pancreatic necrosis of >50% is a major risk factor for pancreatic infection following acute pancreatitis. Primary organ failure predicts development of infective pancreatic infection in patients with acute pancreatitis.

Evidence Statement

Gram-negative organisms are the most common organisms isolated from infected pancreatic necrosis following acute pancreatitis in Indian patients. Prophylactic antibiotic use in patients of AP to prevent IPN has been associated with increased risk of infection with gram-positive organisms. Resistance to carbapenems, beta-lactam /beta- lactamase inhibitors and quinolones in gram-negative organisms isolated from IPN has increased, however, with maintain sensitivity to colistin and tigecycline.

What are the Empirical Antibiotics if Choice for Treatment of Pancreatic Infection Following Acute Pancreatitis?

Evidence Statement

Prophylactic use of antibiotics in patients with necrotizing pancreatitis has not been shown to reduce incidence of pancreatic infection and mortality. The presence of persistent fever, leukocytosis, multiorgan failure and presence of air within pancreatic necrosis suggest infected pancreatic necrosis. Cephalosporins, piperacillin-tazobactam, quinolones and carbapenems have the highest whereas aminoglycosides have the lowest penetration into necrotic pancreatic tissue. Response to antibiotic therapy is assessed by clinical and radiological parameters.

Recommendation

- Routine use of prophylactic antibiotics to prevent pancreatic infection following acute pancreatitis of any severity is not recommended (1A).
- Empirical antibiotic regimen in patients with infected pancreatic necrosis should be guided by local microbiological data, susceptibility pattern, pharmacokinetic property of antibiotics and previous antibiotic exposure (UPP).

- In treatment-naïve patients with evidence of infected pancreatic necrosis, we recommend empirical treatment with either carbapenems, piperacillin-tazobactam or cefoperazone-sulbactam (2A).
- In patients not responding or already exposed to the piperacillin-tazobactam, cefoperazone- sulbactam or carbapenems, colistin should be added to the empirical regime (3B).
- Duration of antibiotic therapy should be guided by clinical, radiological and laboratory parameters (UPP).
- Patients not responding to antibiotics should undergo necrosectomy and drainage (3B).

Biliary Sepsis, Acute Cholangitis

What are the Incidence, Risk Factors, and Microbiology of Biliary Infection in ICU?

Evidence Statement

Incidence of acute cholangitis varies with underlying etiology and ranges from 0.2 to 10%. Cholelithiasis, choledocholithiasis, benign and malignant common bile duct (CBD) strictures, CBD interventions, and stenting are the most common risk factors for cholangitis.

Evidence Statement

Gram-negative organisms are the most common organisms isolated from patients with acute cholangitis. Most of the pathogens isolated are susceptible to third-generation cephalosporins (such as cefoperazone-sulbactam), aminoglycosides, quinolones, ureidopenicillins, and carbapenems. Risk factors for multidrug drug resistance organisms causing acute cholangitis include an indwelling biliary stent, malignant biliary obstruction, previous hospitalization, and antibiotic use within 90 days.

What is the Empirical Antibiotic Regimen for Acute Cholangitis?

Evidence Statement

The empirical antibiotic regime in patients with acute cholangitis is guided by the severity of the disease, local antibiotic susceptibility pattern, and biliary penetration of the antibiotics. The duration of antibiotics depends on the severity of cholangitis and adequacy of source control. Biliary drainage (percutaneous or endoscopic) is required in addition to antibiotic use in the management of acute cholangitis.

Recommendation

- Empirical antibiotic therapy should be guided by the severity of the cholangitis, local microbiological susceptibility patterns, biliary penetration of antibiotics, and previous antibiotic exposure (UPP).
- We recommend either beta-lactam/ beta-lactamase inhibitor (such as cefoperazone-sulbactam or piperacillin/tazobactam) or carbapenems (imipenem/meropenem) as monotherapy in patients with moderate to severe cholangitis (3B).
- We recommend antibiotic duration for 4-7 days in patients with acute cholangitis after adequate source control (2B).
- Biliary drainage should be considered in all patients with cholangitis in addition to empirical antibiotic therapy (1A).
- Anti-anaerobic therapy (such as metronidazole, tinidazole, or clindamycin) is required if a biliary-enteric anastomosis is present and the primary antibiotic therapy does not include carbapenems, piperacillin/tazobactam, or cefoperazone/sulbactam as these drugs have sufficient anti-anaerobic activity. (3A)

Liver Abscess

What are the Most Common Organisms Causing Liver Abscess in ICU?

Evidence Statement

Amoebic liver abscess is the most common cause of liver abscess in Indian setup. The incidence of pyogenic liver abscess varies from 2.3 to 446 per 100000 hospital admissions per year. Gram-negative organisms (*E. coli* and *Klebsiella*) are the most common organisms causing pyogenic liver abscess. Risk factors for pyogenic liver abscess include diabetes mellitus, older age, male gender, biliary diseases, biliary procedures, alcoholism, malignancy, intra-abdominal infection, and cystic lesions in the liver.

What are the Empirical Antibiotics of Choice for Treating Liver Abscess in ICU?

Amoebic Liver Abscess

Evidence Statement

Metronidazole is the drug of choice for the treatment of amoebic liver abscess. The optimum duration of treatment in patients with amoebic liver abscess is 7-10 days. Routine needle aspiration of amoebic liver abscess is controversial. Addition of aspiration to drug therapy in patients with amoebic liver abscess of >5 cm in size hastens clinical improvement.

Recommendation

- We recommend metronidazole as an initial antibiotic of choice in patients with amoebic liver abscess (2A).
- We recommend antibiotic treatment for a period of 7-10 days in patients with amoebic liver abscess (3B).
- Needle aspiration of amoebic liver abscess is recommended in patients with a lack of clinical improvement in 48-72 hours, left lobe abscess, abscess more than 5-10 cm or thin rim of liver tissue around the abscess (<10 mm) (UPP).
- The luminal agents used to remove any intraluminal cysts (paromomycin, diiodohydroxyquin or diloxanide furoate) should be used even if the stool microscopy is negative (UPP).

Pyogenic Liver Abscess

Evidence Statement

Beta-lactam/beta-lactamase inhibitors, metronidazole, and carbapenems are effective antibiotics for management of pyogenic liver abscess. Carbapenems are effective in case of suspected infection with ESBL producing organisms or melioidosis. Antibiotics are required for prolonged periods ranging from 4-6 weeks. Clinical and radiological assessment is required to guide the adequate treatment duration. Initial 2-4 weeks therapy may be parenteral while oral therapy may be given for rest of the duration.

Recommendation

- We recommend beta lactam/beta lactamase inhibitors with metronidazole in patients with pyogenic liver abscess for a duration of 4-6 weeks (2A).

- We recommend carbapenems in case of infection with ESBL-producing organisms or melioidosis (2B).
- The empiric regimen should also cover *E. histolytica* until the causative pathogen is found or amebic abscess is excluded (UPP).

Peritonitis

What are the Most common Organisms Causing Peritonitis in ICU?

Evidence Statement

The risk factors for development of primary peritonitis are decompensated cirrhosis, nephrotic syndrome and peritoneal dialysis. The risk factors for development of secondary peritonitis include intra-abdominal organ perforation, post intra-abdominal surgery, and trauma. Longer ICU stay, urgent operation on hospital admission, total parenteral nutrition, and stomach-duodenum as primary infection site are associated with the development of tertiary peritonitis. Gram-negative enteric organisms (such as *E. coli*, and *Klebsiella pneumoniae*) are the common causes of primary and secondary peritonitis. Other organisms include gram-positive as well as anaerobic bacteria. The organisms commonly isolated in tertiary peritonitis are *Candida*, Enterococcus faecium and *Staphylococcus* epidermidis.

What are the Empirical Antibiotics of Choice for Treating Peritonitis in ICU?

Primary Peritonitis

Evidence Statement

Third-generation cephalosporins are the most effective antibiotic therapy for primary peritonitis. Antibiotics are usually required for 7-10 days for adequate treatment. Most of the organisms isolated in secondary peritonitis are sensitive to beta-lactam/beta-lactamase inhibitors or carbapenems. For gram-positive organisms, vancomycin and linezolid are effective treatment options. Short duration of antibiotic treatment (4 days) is as effective as a longer duration after adequate source control.

Recommendation

- We recommend third generation cephalosporins (such as cefotaxime and ceftriaxone) for a duration of 7-10 days in patients with primary peritonitis (2A).
- We recommend either beta-lactam/beta-lactamase inhibitor or carbapenems with an anaerobic cover (using metronidazole) for the treatment of secondary peritonitis (2A).
- For secondary peritonitis, antibiotic treatment is required for at least 4 days after an adequate source control; however, longer treatment is required if adequate source control is not achieved (2A).

CNS Infections in ICU

What are the Most Common Organisms Causing Acute Bacterial Meningitis in ICU?

Community-acquired Meningitis

Evidence Statement

The incidence of community-acquired pyogenic meningitis ranges from 2 to 7.40 per lakh population and data suggest higher incidence in children. The common causative organisms include *Streptococcus pneumoniaee*, *Neisseria meningitidis*, other *streptococci*, *Haemophilus influenzae* and *Listeria monocytogenes*. Other causative organisms are *staphylococcus* species, gram-negative bacilli, and *Pseudomonas*. Common risk factors for community-acquired bacterial meningitis are otitis media, elderly population, depressed immune status and prior use of antibiotics.

Nosocomial Meningitis

Evidence Statement

Incidence of post-ventricular drain or catheter meningitis ranges from 2% to 27%. Commonly implicated organisms are CONS (especially *staphylococcus* epidermidis), *Staphylococcus aureus*, *Acinetobacter*, *pseudomonas*, and *Enterobacter*iaceae. Risk factors are repeated catheterization, higher catheter duration, CSF sampling, presence of concomitant systemic infection, and surgical technique i.e., subcutaneously tunneled extraventricular drain (EVD), Rickham reservoir with percutaneous CSF drainage. The incidence of post craniotomy or post neurosurgery meningitis is 0.02% to 9.5%. Most commonly implicated organisms are *Staphylococcus aureus*, coagulase-negative staphylococci (especially S. epidermidis), *Enterobacter*iaceae, *Acinetobacter*, and *pseudomonas*. Risk factors include CSF leak, EVD, longer duration of drainage, multiple operations, lack of antibiotic prophylaxis, and emergency surgery. The incidence of post-neuroaxial blockade meningitis is 0.2 per 10000 with *Viridans streptococci* and *Staphylococcus aureus* being common organisms. Exogenous inoculation is the main risk factor. Post-head trauma meningitis incidence ranges from 1.39% to 2% with CONS, *Acinetobacter*, and *Enterobacter*iaceae as common microbes and prolonged hospitalization, and insertion of a lumbar and ventricular drain as common risk factors. Post-internal ventricular drain infection incidence ranges from 5.9% to 15.2%. The most common causative organisms are CONS, *Staphylococcus aureus*, gram-negative bacilli, group D *streptococci*, and *Propionibacterium acnes*. CSF leak, single gloves use, and number of times shunt exposed to breached surgical gloves are the risk factors.

What are the Empirical Antibiotics of Choice for Treating Acute Bacterial Meningitis in ICU? What should be the Duration of Antibiotic Treatment?

Community-acquired Meningitis

Evidence Statement

Choice of antibiotics depends on the most likely causative microorganisms, local antibiotics sensitivity patterns, mechanism of infection, and patient's predisposing condition. Most commonly recommended empirical antibiotic regimens include third-generation cephalosporin plus vancomycin, third-generation cephalosporin monotherapy and penicillin monotherapy. Addition of amoxicillin, ampicillin or benzyl-penicillin has been recommended in patients older than 50 years. However, antibiotic therapy should be modified according to the isolated organisms since MDR organisms are being reported from community as well.

Recommendation

- We recommend third-generation cephalosporin (preferably ceftriaxone) plus vancomycin as empirical antibiotics of choice for community-acquired meningitis (3A).
- We recommend adding ampicillin or amoxicillin if the age >50 years (3A).

- If beta-lactams are contraindicated, we recommend chloramphenicol plus vancomycin as the antibiotic of choice, and to add cotrimoxazole if age >50 years (3A).
- We recommend ciprofloxacin or aztreonam plus vancomycin as an alternative regimen and to add cotrimoxazole, if age greater than 50 years (UPP).
- We recommend the duration of antibiotics based on suspected or isolated organisms i.e., 10 to 14 days for *Streptococcus pneumoniaee*, 14 to 21 days for *Streptococcus agalactiae*, 7 days for *Neisseria meningitidis* or *Haemophilus influenzae*, 21 days for aerobic gram-negative bacilli, and 21 days or more for *Listeria monocytogenes* (3A).
- If no microorganism is identified, antibiotics should be given for at least 10 to 14 days (3A).

Nosocomial Meningitis

Evidence Statement

Vancomycin in combination with cefepime, ceftazidime or meropenem is a commonly recommended empirical antibiotic regimen for nosocomial meningitis. Alternative regimens include third-generation cephalosporin or meropenem monotherapy or ceftriaxone plus flucloxacillin or cloxacillin combination therapy. Limited available evidence shows the efficacy of intraventricular or intrathecal antibiotics in the management of nosocomial meningitis poorly responsive to systemic antibiotics.

Recommendation

- We recommend vancomycin *plus* cefepime or ceftazidime or meropenem as empirical antibiotics of choice for nosocomial meningitis (3A).
- Colistin may be given if the incidence of CRE or drug-resistant *Acinetobacter* is high in the specific unit (UPP).
- If beta-lactams are contraindicated, we recommend replacing beta-lactam with aztreonam or ciprofloxacin (3A).
- Intraventricular or intrathecal antibiotics should be considered if infection responds poorly to appropriate systemic antibiotics clinically or microbiologically (3A).

What are the Most Common Organisms Causing Brain Abscess in ICU?

Evidence Statement

Incidence of brain abscess ranges from 1.3 to 2.6 cases per lakh population. Most commonly involved micro-organisms include *streptococcus* (especially *S. viridans*), *staphylococcus* (especially *S. aureus*), gram-negative bacilli, anaerobes (bacteroides, *Peptostreptococcus*, *Fusobacterium*), *pseudomonas* and *H. influenzae*. Polymicrobial etiology accounts for 23-26% cases. Risk factors include otitis media, sinusitis, head trauma, congenital heart diseases, hematogenous spread, surgery, immunocompromised status, pulmonary disease, meningitis and odontogenic infections.

What are the Empirical Antibiotics of Choice for Treating Brain Abscess in ICU? What should be the Duration of Antibiotic Treatment?

Evidence Statement

The most common empiric treatment consists of a third-generation cephalosporin combined with metronidazole. Antibiotic duration ranges from 4 to 8 weeks.

Recommendation

- We recommend third-generation cephalosporins plus metronidazole as the empirical antibiotic of choice for brain abscess (3A).
- We recommend adding vancomycin if there is a high likelihood of MRSA (3A)
- We recommend vancomycin plus ciprofloxacin if beta-lactams are contraindicated (3A).
- We recommend aztreonam if ciprofloxacin cannot be given or contraindicated (UPP).
- We recommend a minimum 4 weeks of therapy; however, duration may be extended according to clinic-radiological response irrespective of aspiration or excision of abscess (3A).

Skin and Soft Tissue Infections in ICU

What are the Most Common Organisms and Risk Factors for SSTI in ICU?

Evidence Statement

Older age, diabetes mellitus, obesity, malignancy, cirrhosis and longer ICU stay are risk factors for SSTIs. Gram-positive organisms (*Staphylococcus aureus*) are the most common organism responsible for the SSTIs. *E. coli* and *pseudomonas* are common pathogens among gram-negative organisms. MRSA and ESBL producing gram-negative organisms are the most common causative agents for SSTIs in ICU. Monomicrobial necrotizing fasciitis is commonly caused by *Streptococcus pyogenes*; mixed coliforms, anaerobes and staphylococci are common causes of polymicrobial necrotizing fasciitis.

What are the Empirical Antibiotics of Choice for Treating SSTI in ICU ? For Empirical Therapy, should Combination Therapy be Preferred over Monotherapy?

Evidence Statement

Vancomycin, teicoplanin, daptomycin and linezolid are effective in SSTIs caused by MRSA. Piperacillin-tazobactam and carbapenems are the most effective antibiotics for ESBL producing gram-negative organisms. Penicillin plus clindamycin are most effective antibiotics in monomicrobial necrotizing fasciitis, whereas a combination of piperacillin-tazobactam, fluoroquinolone and clindamycin is effective for polymicrobial necrotizing fasciitis.

Recommendation

- For moderate non-purulent SSTI, we recommend intravenous penicillin or clindamycin as first choice of antibiotics (2A).
- Severe non-purulent SSTI should be treated with a combination of piperacillin-tazobactam along with coverage for MRSA (vancomycin, teicoplanin, daptomycin or linezolid) (2A).
- Concomitant surgical inspection or debridement should be considered for severe non-purulent SSTIs (2A).
- For severe purulent SSTI, incision and drainage followed by empiric antibiotics including piperacillin tazobactam, along with MRSA coverage (vancomycin, teicoplanin, daptomycin or linezolid) is recommended (3A).
- Penicillin plus clindamycin is recommended for monomicrobial necrotizing infection caused by *Streptococcus pyogenes* or clostridial species. For polymicrobial necrotizing fasciitis, a combination of piperacillin-tazobactam, fluoroquinolone and clindamycin is recommended (3A).

What should be the Duration of Antibiotic Treatment for SSTI?

Evidence Statement

Shorter course of antibiotic therapy is adequate for uncomplicated SSTIs while complicated SSTIs require longer duration of antibiotic therapy.

Recommendation

- Severe nonpurulent SSTIs should be treated with at least 5 days of antibiotics. (3A)
- Severe SSTIs with organ dysfunction should be treated with a prolonged course of antibiotics of 2-3 weeks duration. (3A)

Sepsis of Unknown Cause in ICU

What is the Empirical Treatment for Sepsis of Unknown Cause in ICU?

Evidence Statement

Empirical therapy with dual class (with different mechanisms of action) combination antimicrobial therapy for sepsis of unknown cause in ICU is associated with have better clinical outcomes. Empirical therapy with either piperacillin-tazobactam or carbapenems in combination with aminoglycoside or fluoroquinolone has been shown to give appropriate broad coverage leading to better clinical outcomes as compared to monotherapy.

Recommendation

- We recommend empirical antimicrobial therapy with combination of ceftriaxone and doxycycline or macrolide for community-acquired sepsis of unknown origin in ICU (UPP).
- We recommend empirical antimicrobial therapy with combination of beta-lactam/beta-lactamase inhibitor and fluoroquinolone or aminoglycoside for nosocomial sepsis of unknown origin in ICU (UPP).
- Empiric therapy should attempt to provide antimicrobial activity against the most likely pathogens based upon clinical features along with local patterns of infection and resistance (UPP).
- Duration of therapy is 7 to 10 days, though longer courses may be appropriate in patients with slow response (3B).

Empirical Antifungals for Non-neutropenic Patients in ICU

What are the Risk Factors for Invasive Fungal Infections in ICU?

Evidence Statement

Risk factors for invasive fungal infections in non-neutropenic patients in ICU are surgery, total parenteral nutrition, renal replacement therapy, cardiopulmonary bypass >120 minutes, diabetes mellitus, central venous catheters, urinary catheters, *Candida* colonization with colonization index >0.5, use of broad-spectrum antibiotics, acute renal failure, mechanical ventilation >3 days and APACHE II score >16.

What is the Role of Empirical Antifungals in Non-neutropenic Patients in ICU?

Evidence Statement

Empirical antifungals for non-neutropenic patients in ICU routinely has not been associated with decrease in mortality or hospital length of stay. Empirical antifungals in patients at high risk for invasive fungal infections in ICU has been shown to reduce incidence of subsequent proven invasive fungal infections.

Recommendation

- We do not recommend the routine use of empirical antifungals in non-neutropenic patients in ICU (1A).
- Empirical antifungals may be considered in critically ill patients with high risk of invasive fungal infections to reduce the incidence of subsequent invasive fungal infections (1B).

What is the Antifungal Agent of Choice and Duration of Empirical Therapy in Non-neutropenic Patients in ICU?

Evidence Statement

Fluconazole and caspofungin are useful as empirical antifungal therapy in non-neutropenic ICU patients at high risk of Invasive fungal infection. In India, rate of fluconazole resistance is up to 7%, especially in non-albicans *Candida* species.

Recommendation

- We recommend fluconazole or caspofungin as preferred empirical antifungal agents in non- neutropenic ICU patients at risk for invasive fungal infection (1A).
- Caspofungin may be preferred in areas with high prevalence of fluconazole resistance (1B).
- Micafungin or anidulafungin may be used as alternative agents (3A).
- Recommended duration of empirical antifungal therapy is 2 weeks (3A).

Antibiotic Stewardship

Does Antibiotic Stewardship Improve Patient Outcome in ICU?

Evidence Statement

Antibiotic stewardship programs in hospitalized patients are associated with reduction in number of antibiotic days, duration of hospital stay and all-cause mortality.

Recommendation

All hospitals should have an antibiotic stewardship program including the intensive care units (1A).

What are the Essential Strategies of Antibiotic Stewardship in an ICU Setting?

Evidence Statement

Antibiotic stewardship requires a multidisciplinary approach with integration of infectious disease physician, microbiologist with logistic and financial support from hospital administration. Both enablement and restrictive strategies are useful in improving adherence to antibiotic stewardship programs. Restrictive strategies give immediate results. Enablement practices are more resource intensive. Most studies have used a combination of both the methods and have shown additive effects. Providing feedback to the treating team improves adherence. A single RCT has shown that restrictive strategy alone may cause delay in initiation of antibiotics.

Recommendation

Prospective audit of antibiotic use and/or preauthorization (if feasible) along with feedback to the treating team is recommended as part of antibiotic stewardship program (1A).

What is the Role of Antibiotic Cycling, Intravenous to Oral Switch and De-escalation in the ICU?

Evidence Statement

Antibiotic cycling in the intensive care unit has not been adequately studied in randomized controlled trials. Non-randomized studies show significant heterogeneity in terms of site of study, method of cycling and confounders like simultaneous infection control measures being employed. Evidence of benefit of antibiotic cycling is lacking, with few studies demonstrating reduction in colonization though mortality and length of hospital stay remain unchanged.

Recommendation

Antibiotic cycling should not be used as a method of antibiotic stewardship program (2A).

Scheduled Intravenous to Oral Switch

Evidence Statement

Early intravenous to oral transition of antibiotics reduce hospital length of stay and cost of care. There is no increase in mortality or other adverse events when this is done after assessing as to which patients can be safely transitioned to oral therapy.

Recommendation

Antibiotic stewardship programs should implement strategies to improve timely transition from parenteral to oral antibiotic therapy (2A).

De-escalation in Intensive Care Unit

Evidence Statement

Pooled results from observational studies in an ICU setting do not show any increase in mortality with antibiotic de-escalation while significantly reducing antibiotic exposure days and ICU length of stay.

Recommendation

Antibiotic de-escalation in the ICU is recommended as part of antibiotic stewardship program (2A).

What is the Role of Procalcitonin in Antibiotic De-escalation in ICU?

Evidence Statement

Implementation of antibiotic de-escalation algorithm based on serial procalcitonin measurements has been shown to reduce mortality, length of ICU stay, total duration of antibiotic days and health care costs.

Recommendation

Procalcitonin based algorithms may be used for antibiotic de-escalation (1A).

Antimicrobial Prescription in Critically Ill Immunocompromised Patients

What should be the Empiric Antibiotic Therapy in Critically Ill Febrile Neutropenic Patients with Suspected Bloodstream Infection?

Evidence Statement

Gram-positive and gram-negative organisms are common causes of febrile neutropenia, with gram-negative organisms predominating in India. The commonly isolated GNBs include *Enterobacter*iaceae (*E. coli* and *Klebsiella* species) and *Pseudomonas aeruginosa* to be the most common among gram-negative organisms. *Staphylococcus aureus* and Coagulase negative *staphylococcus* are most common gram-positive isolates. Recent studies have reported increasing prevalence of MDR organisms. Choice of antibiotics depends on local epidemiology, focus of infection and host and disease characteristics. Current evidence shows carbapenem resistance among *Enterobacter*iaceae is 35-50 %, *Pseudomonas* spp 47% and *Acinetobacter* spp 62%. Acute leukemia patients presenting to the ICU, patient already on carbapenem shifted to ICU from ward, previous multidrug-resistant infections in the last 1 month and patients on vasopressors are at risk of harboring carbapenem resistant organisms. Empiric upfront vancomycin has not been shown to improve clinical outcomes or mortality in febrile neutropenia. Patients at risk of MRSA infections include suspected indwelling catheter infection (rigors following infusion, cellulitis at exit site), skin and soft tissue infection, severe mucositis, culture growing gram-positive cocci pending identification, previous MRSA colonization/ infection and hemodynamic instability at admission.

Recommendation

- In a critically ill febrile neutropenic patient presenting to the ICU with organ failure, empiric antibiotic therapy should be initiated with or escalated to a broad-spectrum carbapenem like imipenem or meropenem (UPP).
- Empiric combination of Meropenem and Colistin/Polymyxin B should be considered in patients having high risk of infection with resistant gram-negative organisms (3A). Following risk factors should be assessed:
  - Critically Ill patients with underlying acute leukemia (on induction or consolidation therapy) presenting to the ICU.
  - Patients of acute leukemia/lymphomas on beta-lactam/beta lactamase inhibitor±aminoglycosides, shifted to ICU from ward.
  - Previous history of infection with multidrug-resistant organism in last 1 month.
  - Hypotensive patients requiring vasopressor infusions (refractory septic shock).
  - Patient shifted to the ICU on carbapenem therapy.
- We strongly caution against the use of empiric combination of Meropenem and Colistin/Polymyxin B or Colistin/Polymyxin B alone in patients who are not high risk of infection with carbapenem resistant gram-negative organisms as defined above (3A).
- We caution against use of other carbapenems like Doripenem and Ertapenem due to lack of positive evidence and inadequate spectrum respectively (2A).
- Vancomycin/Teicoplanin should be added as empiric therapy in critically ill febrile neutropenic patient with risk factors for MRSA infection (3A). These include:
  - Suspected indwelling vascular catheter infection.
  - Skin and soft-tissue infection.
  - Previous colonization/infection with methicillin-resistant *Staphylococcus aureus*.
  - Blood Culture growing gram-positive cocci awaiting identification.
  - Severe mucositis.
  - Hemodynamic instability(hypotension) at admission from home or outpatient department (UPP).
- Empiric MRSA coverage should be avoided in absence of risk factors for MRSA and in ICUs with low prevalence of MRSA(UPP).
- After the initiation of empiric therapy based on the factors listed above, the subsequent therapy should be based on the organisms

isolated and sensitivity patterns. In patients with no isolates, the treatment should be continued as per the response to ongoing antibiotics and appearance of any new focus of infection (UPP).

What Methods should be Used for Early Identification of Causative Organisms in Febrile Neutropenia Patients?

Evidence Statement

Two sets of blood cultures drawn prior to antibiotic administration yields microbiologic diagnosis in 30% cases. Addition of multiplex PCR techniques can aid in early diagnosis and has high sensitivity and specificity as compared to culture-based methods.

Recommendation

- We recommend collection of at least 2 sets of blood cultures, with a set collected simultaneously from peripheral site and one central. In case of multi lumen catheter, one set per lumen should be collected (1A).
- Two blood culture sets from separate venepunctures should be sent if no central venous catheter is present (1A).
- One set includes one aerobic and one anaerobic culture bottle. Blood culture volume should be at least 10 mL/bottle (1A).
- The use of molecular methods for identification of multidrug-resistant organisms and their antibiotic sensitivity pattern can be considered in critically ill patients, however, the availability and cost may be a concern along with risk of false negativity and false positivity (2B).

What should be the Approach to Empiric Antifungal Therapy in Febrile Neutropenia in Critically Ill Immunocompromised Patients?

Evidence Summary

Patients with febrile neutropenia are at risk of developing invasive fungal infections. IFIs have high mortality in patients with febrile neutropenia. Persistent or recurrent febrile neutropenia and development of lung infiltrates may be clues to fungal etiology of febrile neutropenia. Yeast (primarily *Candida* species) and molds are common etiologic agents. In patients with persisting fever without any localization, empiric antifungals targeting *Candida* species are initiated. Chest radiograph has poor sensitivity for *pneumoniae* detection in patients with febrile neutropenia, and CT Chest is preferred. Galactomannan assay is highly specific for *Aspergillus* species with some cross-reactivity with *Histoplasma capsulatum* and Penicillium species. False-positive reaction can occur with concomitant use of b-lactam/b-lactamase combinations, such as piperacillin/tazobactam. Use of Beta-D Glucan alone has limited sensitivity for the diagnosis of invasive candidiasis. Invasive aspergillosis should be suspected in patients with persistent febrile neutropenia with the development of signs of *pneumoniae* including lung infiltrate.

The echinocandins have demonstrated significant fungicidal activity and treatment success against most of the *Candida* species in randomized clinical trials. Individual echinocandins namely caspofungin, micafungin and anidulafungin have similar efficacy and are interchangeable. Echinocandins have poor penetration in eye, CNS, and urine. Echinocandins are not active against Zygomycosis. Voriconazole is the preferred agent for invasive aspergillosis, whereas liposomal amphotericin B is preferred for zygomycosis. Echinocandins have been useful in salvage therapy of aspergillosis. Guidelines advise to continue treatment for candidemia for at least two weeks after 2 weeks after documented clearance of *Candida* from the bloodstream, and resolution of neutropenia and symptoms attributable to candidemia. Recommended duration of invasive pulmonary aspergillosis is 6-12 weeks based on the resolution of symptoms and neutropenia. Combination antifungal treatments have limited evidence for added efficacy.

Recommendation

- Following patients should be considered for initiation of antifungal therapy when they present to ICU with shock or respiratory distress especially when they have persistent or recurrent fever or clinical deterioration after >3 days of broad-spectrum antibiotics (2A).
  - Allogenic HSCT.
  - Severe mucositis with diarrhea.
  - Prolonged/anticipated duration of neutropenia >10 days.
  - Worsening on broad-spectrum antibiotics like BL/BLI and Carbapenems.
  - More than 2 weeks of high-dose steroids (more than 15-20 mg of prednisolone or equivalent).
  - History of invasive fungal infection.
  - New onset lung infiltrate. (Since chest x ray has low sensitivity, HRCT should be done in these patients).
- We recommend the use of caspofungin (echinocandin group) as initial antifungal therapy. Caspofungin should be avoided in patients with chronic liver disease (Child-Pugh C) (2A).
- Anidulafungin and Micafungin can be considered if there are contraindications to use of caspofungin (3A).
- Voriconazole is the drug of choice for proven, probable or possible aspergillosis. Due to its variable bioavailability voriconazole should be administered IV. In patients with renal dysfunction caspofungin can be given instead of IV voriconazole (1A).
- Liposomal Amphotericin B is the drug of choice for suspected or confirmed Mucormycosis (1A).
- All efforts should be made to confirm presence of invasive fungal infection with the use of tests including CT Chest/suspected site (abdomen for hepatosplenic candidiasis or mucormycosis/paranasal sinus for mucormycosis), β –D- glucan, serum and BAL Galactomannan, fungal culture. Tissue (lung/other clinically involved sites) biopsy should be performed if required, whenever feasible and safe (1A).
- We do not recommend routine use of combination antifungal therapy for probable or proven Invasive aspergillosis (IA) due to lack of strong evidence (3A).

Which Patients should be Considered for Empiric Treatment against *Pneumocystis jirovecii* Pneumoniae?

Evidence Statement

HSCT, high dose corticosteroids, T-cell depleting agents and rituximab predispose to PCP infection. Hypoxemia and characteristic radiologic abnormalities indicate PCP *pneumoniae*, though chest radiograph might be normal in early disease. Empiric treatment with trimethoprim-sulfamethoxazole is indicated in suspected PCP *pneumoniae*.

Recommendations

- Treatment with sulfamethoxazole/trimethoprim should be considered in high risk patients such as allogenic HSCT, high-dose corticosteroid therapy administration of T-cell-depleting agents such as fludarabine/purine analogues and rituximab when such patients present with hypoxemic respiratory failure

with or without radiological evidence of Pneumocystis carinii *pneumoniae* especially if they are not on PCP prophylaxis (3A).
- Every attempt should be made to confirm PCP infection (3A).

What is the Role of Empiric Antiviral Therapy in Immunocompromised Patients with Febrile Neutropenia?

Evidence Statement

Antiviral therapy in febrile neutropenia is given according to treatment guidelines of the etiologic agent. There are no effective agents for treatment of parainfluenza and respiratory syncytial virus infection at present.

Recommendations

- There is no role of empirical antiviral therapy with febrile neutropenia. Active HSV or VZV infections in neutropenic patients indicated by clinical or laboratory evidence should be treated with Acyclovir (3A)
- Immunoglobulin tests should not be used to diagnose VZV or HSV infection (3A).
- Ganciclovir is recommended for the empiric therapy for CMV in patients with high risk of CMV reactivation (3A):
  - Administration of T-cell-depleting agents such as fludarabine/purine analogues, rituximab
  - Patients on high dose steroids who develop diarrhea
  - *Pneumoniae* not responding to antibiotics & antifungals.
- No specific treatment for infections with RSV and parainfluenza viruses due to lack of specific evidence (3A).

What is the Role for Empiric Antimicrobial Therapy for Tropical Infections like Malaria, Leptospirosis in Patients with Febrile Neutropenia?

Evidence Statement

There is insufficient evidence regarding tropical infections in patients with hematologic or solid organ malignancies and febrile neutropenia.

Recommendation

- There is no role for empirical antimicrobial therapy against tropical infections like malaria, leptospirosis in febrile neutropenia patients (3A).
- Documented tropical infections in neutropenic patients in ICU should be treated similar as they are treated in non-neutropenic patients (UPP).

What is the Role of Surveillance Cultures in Guiding Therapy in Febrile Neutropenia Patients?

Evidence Statement

Surveillance cultures have not been shown to correlate with subsequent causative organisms in immunocompromised patients.

Recommendation

- We strongly recommend against repeated surveillance cultures as these do not help to guide antibiotic therapy (3A).

What is the Role of Source Control in the Treatment of a Febrile Neutropenic Patient?

Evidence Statement

Source control at the earliest possible time reduces microbiologic burden and improves outcomes. Source control includes debridement, drainage of collections, removal of incriminated indwelling catheters and implanted devices.

Recommendations

We recommend that in patients with febrile neutropenia with clinically documented source of infection (as defined below), immediate intervention should be undertaken for source control (3A).

What should be the Approach to Antibiotic De-escalation in Patients with Febrile Neutropenia?

Evidence Statement

Antibiotic de-escalation to definitive therapy is feasible after identification of causative organism or in patients who remain afebrile for >48 hours with evidence of marrow recovery.

Recommendations

Antibiotic de-escalation should be considered in the following situations (3A):
- Once and if a pathogen is identified, we recommend de-escalation to an antibiotic that the organism is susceptible to.
- Treat with appropriate agents based on the site and pathogen until the patient is afebrile for at least 48 hours and there is evidence of marrow recovery (neutrophil count ≥500 cells/mm^3).
- In patients without microbiologically documented infection continue empirical antimicrobials until the patient is afebrile for at least 48 hours and there is evidence of marrow recovery (neutrophil count ≥500 cells/mm^3)

Which Antibiotics should be Used for Febrile Neutropenia due to Multidrug-resistant Bacteria?

Evidence Statement

Antibiotics like fosfomycin, tigecycline and minocycline have activity against variety of MDR gram-negative organisms. For MRSA, vancomycin, teicoplanin and linezolid have most evidence. Linezolid is effective against vancomycin-resistant enterococci. However, good quality RCTs for MDR infections are lacking in immunocompromised patients.

Recommendation

- Antibiotics like Fosfomycin, tigecycline and minocycline may be considered in infection with multidrug-resistant bacteria in presence of *in vitro* susceptibility after considering the in vivo penetration at source of sepsis, and if alternate agents with proven efficacy are not available or contraindicated (3A).
- Vancomycin or linezolid can be used in cases of MRSA (1A).

Antimicrobial Guidelines in Solid Organ Transplant Recipients

What are the Common Infections in Post-solid Organ Transplant Patients? What should be the Preferred Approach to Empiric Therapy and Diagnostic Evaluation?

Evidence Statement

Incidence of sepsis in solid organ recipients ranges from 20% to 60% and is associated with in-hospital mortality of 5% to 40%. Nosocomial infections predominate in the first month, opportunistic infections till six months posttransplant and subsequently community-acquired infections become most

common. In the Most of these infections are of bacterial followed by fungal etiology. Most common site remains urinary tract infection, followed by line related infections, and *E. coli* the most common etiology. CMV is most common infection from 1 month up to 3 months, whereas tuberculosis reactivation is more common from 3 months to 1 year posttransplantation. Pneumocystis and *aspergillus* infections are common after 1 year. MDR GNB isolates are increasing in prevalence, especially in nosocomial infections. Risk for developing sepsis with bacteremia can be lowered significantly by antibiotic prophylaxis. Prophylaxis is governed by type of transplant and risk of specific infections. Liver transplant patients often receive antibiotics covering skin flora, *enterobacter*iaceae, enterococci and anaerobes whereas post-lung transplant, prophylaxis is against molds, gram-negative bacteria or colonizers. Post-kidney transplantation trimethoprim-sulfamethoxazole given for PJP prophylaxis reduces UTI and bacteremia. Alternatives include nitrofurantoin and cephalexin. Fluoroquinolones increase risk of resistant infections like *pseudomonas*, and should be used with caution. Opportunistic infections have decreased due to anti-infective prophylaxis for CMV and PJP. TMP-SMX provides protection against *toxoplasma*, and protects against UTI, *Listeria* meningitis and *nocardia*l infections.

Recommendation

Anti-infective Prophylaxis

- Prophylaxis in first month posttransplant should depend upon the nosocomial infections, colonization of donor and recipient, and the organ transplanted (1A).
- Trimethoprim-sulfamethoxazole (TMP-SMX) for primary prophylaxis for urinary tract infection (UTI) in renal transplant patients is recommended; TMP-SMX usually given for 6 months for PJP prophylaxis decreases UTI and bacteremia in renal transplant recipients (1A).
- Primary prophylaxis for UTI with agents other than TMP-SMX may be limited to the first month after transplant (3B).

Approach to Diagnosis and Treatment of Infection

- Infections in the first month (0–30 days) of post SOT period should be investigated and treated similarly to those of non-immunocompromised postoperative patient (1A).
- Infections in the first month (0–30 days) of post SOT period should be investigated and treated on the lines of nosocomial infections/ donor derived infections (1A).
- Complete blood count with differential, liver and renal function tests, serum electrolytes should be obtained in all patients with suspected infection (3A).
- We recommend obtaining blood cultures at presentation and preferably prior to initiation of antibiotics in all patients presenting with features suggestive of infection (3A).
- Antimicrobials should be administered considering prior cultures, local antibiogram and susceptibility patterns (1A).
- Asymptomatic bacteriuria (AB) should not be treated (1A) unless same pathogen has been isolated twice consecutively >105 CFU/mL in first 2 months post SOT (2B) or AB is found in Post-kidney transplant recipients. (1B).
- Multidrug-resistant (MDR) urinary tract infection (UTI) with gram-negative bacteria such as *Pseudomonoas* spp and *Klebsiella* spp, newer agents like ceftazidime-avibactam can be considered as alternatives to colistin or aminoglycosides. (1B).

Approach to Diagnosis and Treatment of Respiratory Infection

Evidence Statement

Acute respiratory failure (ARF) following SOT can be due to variety of infective and noninfective causes. Patterns of involvement on chest radiograph or CT scan can help to narrow down diagnosis. Ground glass opacities and micronodular infiltrates can suggest PJP or CMV, whereas lobar consolidation suggests bacterial etiology. Nodular infiltrates suggest fungal, tubercular or malignant etiology. Majority of cases of community-acquired *pneumoniae* have been seen after 6 months posttransplantation. Early initiation of antibiotics after sending blood cultures in patients with septic shock leads to better outcomes. Organisms responsible for CAP include viruses, bacteria, fungal and *mycobacteria*. *Streptococcus pneumoniaee* has been reported to be most common bacteria causing CAP, whereas *P. aeruginosa* was the most common microorganism isolated in nosocomial *pneumoniae*. Bronchoscopic BAL leads to microbiologic diagnosis in up to 77% cases. CT Guided biopsy has been used for diagnosis of patients with lung nodules. Open lung biopsy has been reported to have high yield (85%) but with increased risk of complications. Empiric antimicrobial therapy for *pneumoniae* in SOT patients would depend upon the net state of immunosuppression, the epidemiological exposures, the clinical and radiological profile of the patient, and the local antibiogram.

Recommendation

- We recommend obtaining chest radiograph in all patients with suspected *pneumoniae* (2A).
- We recommend performing a chest computerized tomography (CT) scan in all SOT patients with *pneumoniae* (I,A) and high resolution CT (HRCT) scan in patients with nodular infiltrates with suspected invasive aspergillosis (1A).
- We recommend obtaining nasopharyngeal swab for influenza virus testing by PCR if seasonally appropriate and high suspicion for viral *pneumoniae*(1A).
- Early BAL should be considered in SOT patients with suspected *pneumoniae* admitting to ICU (1A).
- We recommend BAL in patients with pulmonary infiltrates not improving on empiric antimicrobial therapy or in whom there is diagnostic uncertainty on non-invasive testing (1A).
  - BAL fluid should be tested for:
    - Stains and immunohistochemistry- Gram stain, KOH/ Calcofluor white, Auramine-rhodamine, auramine-o, or ziehl-neelson, Modified acid-fast stain, Silver methenamine stain, Galactomannan assay (<0.5 Negative predictive value, >3 positive predictive value).
    - Polymerase chain reaction (PCR)- *Mycobacterium tuberculosis* (Cartridge Based Nucleic Acid Amplification Test (CB-NAAT or GeneXpert), Multiplex PCR assay [(Including Respiratory viruses, CMV)(Quantitative or semiquantitative detection- particularly bacterial)].
    - Culture- Aerobic culture for bacteria, *mycobacteria*l growth indicator tube (MGIT) for *Mycobacterium tuberculosis*, fungal culture.
- Following organisms are diagnostic of infections. If identified, they are less likely to be the contaminants/ colonizers and should be treated: Pneumocystis carinii, *Toxoplasma gondi*i, Strongyloides stercoralis, *Legionella pneumophila*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Mycobacterium tuberculosis*,

Mycoplasma pneumoniaee, Influenza a and b viruses, Respiratory syncytial virus. (2A)

- Open/ Video-assisted thoracoscopy (VATS)/ CT guided/ transbronchial biopsy should be done in patients with lung infiltrates where the non-invasive testing/ BAL haven't been able to provide the diagnosis and who have failed to respond to therapy, after risk-benefit assessment on case to case basis (2A).
- Any prior microbial colonization or antimicrobial resistance pattern of particular organisms should be considered while deciding empiric treatment for *pneumoniae* in SOT patients, particularly so in case of colonization of airway in lung transplant patients (3A).
- Empiric antibiotic therapy with carbapenem based on local susceptibility patterns for suspected community-acquired bacterial *pneumoniae* along with coverage of atypical / intracellular pathogens like *Mycoplasma pneumoniaee*, *Chlamydia pneumoniae*, and *Legionella* spp. is recommended (2A). For the coverage of latter, among macrolides, consider using azithromycin instead of clarithromycin or erythromycin because of its relatively less likelihood to interact with immunosuppressants.
- For suspected viral *pneumoniae*, adding antiviral for influenza should be considered (2A).
- We recommend empiric treatment of recipients requiring hospitalization for *pneumoniae* with broad-spectrum antibiotics (carbapenem ± antipseudomonal ± anti MRSA) depending on local flora and resistance patterns, along with coverage for atypical organisms (2A).
- Antipseudomonal agent/ polymyxin should be added if the patient is admitted in the hospital for ≥48 hours before symptoms (nosocomial *pneumoniae*) (2A), visited medical care (hemodialysis, wound care, immunosuppressants) within the previous 30 days, or hospitalized in an acute care hospital ≥2 days within the prior 90 days (UPP).
- Empiric antifungal therapy may be initiated where there is strong suspicion based on the clinical and radiological profile of the patient (3B).
- Empiric therapy should be initiated/ modified as per clinical, radiological and microbiological findings and response (2A).

CMV Management

Evidence Statement

CMV reactivation risk is increased in post SOT patients due to immunosuppression induced lymphopenia and lymphocyte anergy. Preoperative CMV-IgG serology of donor and recipient can be used to assess risk and guide prophylaxis. In posttransplant period, CMV DNA using quantitative nucleic acid amplification is the diagnostic modality of choice. Detection of CMV by QNAT in BAL fluid and cerebrospinal fluid (CSF) is feasible. For end organ CMV disease, histopathologic diagnosis is the gold standard. CMV retinitis is diagnosed based on ophthalmologic examination. RT-PCR was a more reliable tool to monitor the response to therapy. Pre-emptive therapy is used for most SOT recipients, however, lung transplant patients should receive prophylaxis. Valganciclovir and intravenous ganciclovir have good efficacy and are used for prophylaxis and disease respectively. Letermovir has been shown to be noninferior to valganciclovir for prophylaxis in post renal transplant patients. Post prophylaxis delayed onset CMV disease occurs in donor positive recipient negative SOT recipients three to six months after completion of antiviral prophylaxis and should be treated with pre-emptive therapy. High dose ganciclovir or foscarnet are effective in empiric reatment of refractory disease, along with cautious reduction in immunosuppression. Immunoglobulins as adjunct therapy have been used in refractory disease.

Recommendation

Antiviral Prophylaxis

- Antiviral prophylaxis should be initiated within 10 days post SOT in all at-risk recipients for prevention of CMV infection/disease (1A).
- Valganciclovir (oral 900 mg once daily) or intravenous ganciclovir (5 mg/kg IV once daily) should be used for prophylaxis in all SOT recipients. Only in Post-kidney transplant patients, high dose oral valacyclovir (2Gram qid) may be used as an alternative agent (1A).
- The duration of prophylactic therapy depends upon the CMV serostatus of the donor (D) and recipient (R) pre-transplant and the specific organ transplanted (Table 5).
- For patients receiving lymphocyte-depleting anti-lymphocyte antibodies (e.g. anti-thymocyte globulin ATG) for rejection, antiviral prophylaxis with valganciclovir or intravenous ganciclovir should be initiated (1A).

Pre-emptive Therapy

- Pre-emptive therapy for prevention of CMV disease in asymptomatic CMV infection in SOT patients (tested weekly post-transplant for up to 12 weeks or longer) with valganciclovir 900mg twice daily or intravenous ganciclovir (5 mg/kg twice daily) should be initiated once the predefined viral load threshold has been achieved, and duration be guided by viral load monitoring (ie, CMV DNAemia or antigenemia below the predefined threshold or not detected) (1A).
- Antiviral prophylaxis is preferred over pre-emptive therapy for prevention of CMV disease heart transplant patients (1A).
- Preemptive therapy is not recommended for prevention of CMV disease in lung transplant patients (1A).

Therapy for CMV Disease

- We recommend CMV DNA by QNAT as the laboratory method of choice for rapid diagnosis of CMV infection in blood after SOT (1A).
- We recommend treatment of CMV disease with intravenous ganciclovir (5mg/kg 12th hourly) or oral valganciclovir (900 mg twice daily) (in renally adjusted dosages) (1A).
- For severe or life-threatening CMV disease, very high viral load, and doubtful gastrointestinal absorption, use of intravenous ganciclovir is recommended (1A).
- Oral valganciclovir is an effective initial therapy for mild to moderate CMV disease (I, A), or as a step down to intravenous ganciclovir after clinical improvement (2B).
- Foscarnet and cidofovir can be used only as second-line agents for SOT recipients (due to high risk of nephrotoxicity associated) who are unable to tolerate intravenous ganciclovir or valganciclovir (2A).
- We recommend against use of acyclovir, valacyclovir, and oral ganciclovir for treatment of CMV disease (1A).
- We recommend a duration of treatment with antiviral for a minimum of two weeks and till there is resolution of clinical signs

along with viral clearance as tested by weekly CMV quantitative NAT (QNAT: polymerase chain reaction- PCR) (1A).
- After completion of full-dose antiviral treatment, a 1 to 3 months course of secondary prophylaxis may be considered depending on the clinical situation (2B).
- We recommend monitoring complete blood count with differential and serum creatinine weekly for assessment of potential hematologic and renal toxicity (1A).
- The drug dosage of antiviral should be adjusted as per the renal function test (1A).
- The drug dosage of antiviral should not be decreased due to neutropenia or pancytopenia (1A). Hematopoietic growth factors may be used to counter the myelosuppressive effect of the drugs.
- Cautious reduction in immunosuppression should be considered in SOT patients presenting with CMV disease, especially if the disease is moderate to severe, or with severe lymphopenia or with refractory/ resistant CMV disease (2B).
- Empiric treatment of suspected resistant CMV disease include high-dose intravenous ganciclovir (up to 10 mg/kg q12 hours, renally adjusted) or foscarnet. Definitive antiviral treatment should be guided by results of genotypic testing (2B).
- CMV immunoglobulin or IVIg may be used as an adjunct to antiviral drugs in transplant recipients with life-threatening disease, CMV pneumonitis or resistant CMV disease (2B).

Tuberculosis (TB) in SOT Recipient

Evidence Summary

Incidence of tuberculosis is higher as compared to general population. Up to 50% cases of tuberculosis can bre disseminated or extrapulmonary in post SOT patients. Atypical clinical presentations, less sputum positivity and false negative tuberculin and IGRA tests lead to delays in diagnosis. Radiological investigations like CT scan along with bronchoscopy, BAL or histopathologic evaluation from involved site are needed for prompt diagnosis. Rifampin containing regimens reduce serum concentrations of tacrolimus, cyclosporine, sirolimus and everolimus, whereas rifampin free regimens increase the duration of antitubercular therapy.

Recommendation

- The diagnosis of active TB in transplant recipients requires a high index of suspicion. Although the diagnostic modalities and treatment of TB in SOT patients remains the same as that in immunocompetent hosts, these individuals often require an invasive procedure, such as bronchoscopy with BAL or lung biopsy (1A).
- Rifamycins, particularly rifampin, reduce serum concentrations of tacrolimus, cyclosporine, rapamycin (sirolimus), and everolimus via induction of the cytochrome p450 isoenzyme CYP3A4, necessary dose adjustments, and therapeutic drug monitoring are warranted to avoid development of rejection (II, A). When rifampin is not used, a longer than usual duration of treatment is required (2B).

Infective Diarrhea in SOT Recipient

Evidence Statement

Diarrhea in posttransplant patients can be due to infectious and non-infectious causes. Drug induced diarrhea and infections are most common reported causes. Bacterial infections, parasitic infections (giardiasis) and viral infections (CMV, norovirus) are common infectious causes. Due to frequent exposure to antibiotics and frequent hospitalization, *Clostridium difficile*-associated diarrhea is also common. Stool investigations should be performed for all suspected organisms. The initial management of *C. difficile* infection (CDI) remains similar to non-transplant patients.

Recommendation

- We recommend empiric management of gastrointestinal infections/ diarrhea with ceftriaxone iv + ganciclovir 5mg/kg BD IV and vancomycin 125mg PO QID (if the patient is already on antibiotics to cover CDI) till definitive diagnosis is made (1A).
- If the patient is in septic shock, based on local resistance pattern, and previous drug history of patient consider carbapenems (UPP).
- We recommend cessation of the inciting antimicrobial agent whenever possible (2A).
- We recommend using a NAAT alone or a multistep algorithm for testing (ie, GDH plus toxin; or NAAT plus toxin) rather than a toxin test alone for the diagnosis in stool specimens likely to be having *Clostridium difficile* infection CDI (2A).
- For treatment of CDI in adults, either vancomycin (125mg given 4 times daily orally for adults; 40 to 50mg/kg/day divided QID for pediatric patients, not to exceed adult dosing; for 10-14 days) or fidaxomicin (200mg given twice daily orally for 10 days) is recommended over metronidazole (1A). If these agents aren't available, metronidazole 500 mg 3 times daily by mouth can be used as an alternative.
- We recommend oral vancomycin up to 500 mg orally QID in adults for the treatment of severe/fulminant CDI (I,A). If ileus, consider adding rectal instillation of vancomycin 500 mg in 100 mL normal saline as retention enema 4 times a day (2B).
- Intravenous metronidazole 500 mg intravenously every 8 hours may be administered together with oral or rectal vancomycin (1B).
- In cases of multiple recurrences of CDI, we recommend prolonged courses of oral vancomycin, either in a tapering or pulse dose schedule (2A). Fidaxomicin can be used if available (2B).
- Fecal microbiota transplant (FMT) may be considered in recurrent or relapsing CDI (2B).
- We suggest consideration for surgical intervention in cases of complicated CDI (2B).

Invasive Fungal Infection in SOT Recipients

Evidence Statement

SOT recipients are at increased risk of fungal infections, highest risk in small bowel transplant, followed by lung, liver, heart, pancreas and kidney transplant. Invasive candidiasis is most common fungal infection, followed by aspergillosis, cryptococcosis, non-*aspergillus* molds, endemic fungi and zygomycosis. Emerging *Candida* strains that are drug resistant are a cause for concern and pose challenge in the management. India data is limited, and mucormycosis is the commonest infection. *Candida* infections are most commonly bloodstream infections followed by intraabdominal infections. *Aspergillus* colonization and infection is associated with increased mortality in lung transplant recipients. Various diagnostic modalities including serum markers such as beta-D glucan, galactomannan, imaging (CT scan), bronchoscopic evaluation or histologic evaluation of involved site lead to early diagnosis.

Voriconazole remains the drug of choice for treatment of IA, isavuconazole and lipid formulations AmpB being the alternative agents. Echinocandins can be used as salvage therapy. Isavuconazole is non-inferior to voriconazole for the primary treatment of invasive mold disease caused by *Aspergillus* and other filamentous fungi. Therapeutic drug monitoring (TDM) for azole antifungals (especially voriconazole and posaconazole) improves clinical efficacy and is preferred. For IC or candidemia, echinocandins remain the drug of choice and in a clinically stable patient it can be switched to fluconazole if the *Candida* isolate is susceptible to fluconazole. Duration is dependent on culture negativity and resolution of features of invasive candidiasis.

Recommendation

Invasive Aspergillosis (IA) Treatment

- It is recommended not to use serum galactomannan (GM) to diagnose IA in SOT patients (1A).
- Serum or BAL beta-D-glucan should not be used to screen or diagnose SOT patients for IA (1B).
- BAL GM is the preferred parameter for diagnosis of invasive pulmonary aspergillosis and a value of ≥1.0 in combination with other fungal diagnostic methods is used to diagnose IA in SOT recipients (1A).
- For IA or positive BAL galactomannan, we recommend voriconazole in the dose of 6mg/kg bd for 1 day f/b 3mg/kg bd (1A).
- Isavuconazole and lipid formulations of Amphotericin B (AmB) can be used as alternative agents (1A).
- As a salvage therapy, posaconazole can be used where patients fail to respond or are intolerant to first line agents (1B).
- Echinocandins are not recommended as a primary therapy (1B) and can be used only as a salvage therapy or as a second agent where combination therapy is being considered (3B).
- We recommend therapeutic drug level monitoring (TDM) for voriconazole when using it for the treatment of IA (1A).
- We recommend that treatment be continued for minimum 12 weeks, if tolerated, and guided by clinical and radiological response (1A).

Other Emerging Fungal Infections

- For infection by mucormycetes, lipid formulations of AmB is the drug of choice for induction therapy (1A).
- Posaconazole or isavuconazole can be used as alternative agents for induction and for maintenance therapy (2B).
- Surgical excision or debridement is recommended for all wherever feasible, particularly for mucormycetes infection outside of lungs (2A).
- For trichosporon, azoles are the recommended first line agents (3A), subject to the susceptibility.

Pneumocystis Jirovecii Infection Management

Evidence Statement

Incidence of PJP infections in SOT recipients ranges from 0.6% to 9% in various studies. Risk depends on degree of immunosuppression. PJP infection, in turn, leads to more episodes of rejection and increased need for steroids and immunosuppression. TMP-SMX has high efficacy and availability in both oral and IV preparation with good oral bioavailability. The optimal duration of therapy is usually 14 days which can be extended to 21 days in severe cases with slow clinical improvement. Adjunctive glucocorticoids are recommended for moderate to severe PCP. PJP prophylaxis reduces incidence of PJP in the first year after transplant.

Recommendation

Anti-pneumocystis Prophylaxis

- We recommend anti-pneumocystis prophylaxis to all SOT recipients for 6 to 12 months posttransplant, particularly for centers with incidence ≥3%-5% among transplant recipients (1A).
- Longer duration of prophylaxis may be considered in patients with prior history of PJP (*Pneumocystis jirovecii pneumoniae*) infection, chronic CMV infection, higher intensity of immunosuppression, lung and small bowel transplant recipients, prolonged neutropenia (1A).
- Trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice for prophylaxis of PJP, in a (adult) dose of either 80mg TMP/400 mg SMX (single strength) daily or 160mg TMP/800 mg SMX (double strength) orally three times weekly (1A).

PJP Treatment

- We recommend TMP-SMX as the first-line agent and drug of choice with the Trimethoprim component being 15-20 mg/kg / day in 3 to 4 divided doses (1A).
- In severe infections, if available, intravenous pentamidine probably remains the second-line agent after TMP-SMX (2A). Its usage should be avoided in pancreas transplant recipients (1B).
- Primaquine and clindamycin in combination may be used as alternative in mild to moderate infection. However, primaquine should be avoided in G6PD deficient patients, and association of *clostridium difficile*-associated diarrhea (CDAD) with long term usage of clindamycin should be considered (2B).
- In patients with hypoxemia (PaO_2 <70 mmHg on room air), adjunctive corticosteroids should be administered with antimicrobial therapy, ideally within 72 hours of initiating antimicrobial therapy for maximum benefit (2A). The dose of steroids should be 1 mg/kg/day prednisone (or equivalent) given in two divided doses daily for 5 to 7 days (2A). Steroids should be tapered over a period of 7 to 14 days (2B).
- Duration of antimicrobial therapy should be for at least 14 days (1B).

CNS Infections in SOT Recipients

Evidence Statement

SOT patients with altered sensorium have multifactorial causes and need extensive work up, with MRI being the initial preferred imaging modality. Empirical regimens with bactericidal or fungicidal agents having CNS penetration are initiated at admission, until definitive diagnosis. Common pathogens causing CNS infections in SOT are viral followed by fungal and bacterial agents. Viral meningoencephalitis is most common CNS disease in large prospective studies. Thus, antibiotics covering both gram-positive and gram-negative pathogens along with Acyclovir is part of initial empiric regimen. Amphotericin B plus 5-flucytosine is used as initial treatment of cryptococcal meningitis.

Recommendation

- We recommend initial workup for suspected CNS infections should include (1A)
  - MRI over CT scan.
  - CSF analysis including India ink preparation.
  - Rapid multiplex PCR on CSF.
  - Serum cryptococcal antigen.

- We recommend empiric treatment to be started with Ceftriaxone + Vancomycin + Acyclovir (1A).
- We recommend liposomal Amphotericin B or AmB lipid complex (ABLC) plus flucytosine as the initial treatment for *Cryptococcus* for minimum 2 weeks for CNS disease, disseminated disease, or moderate-to-severe pulmonary disease (1A). Alternatively, liposomal AmB or ABLC can be used for minimum duration of 4 to 6 weeks (1B).

Nocardia in SOT Recipients

Evidence Statement

Nocardia infection can occur post solid organ transplants. Lung transplant patients seem to be at highest risk. TMP-SMX, carbapenems and linezolid have efficacy against *nocardia*. Combination therapy is recommended in critically ill patients with pulmonary, cerebral and disseminated *nocardia*l infection.

Recommendation

We recommend the following regimens for treatment of post-transplant *nocardia* infections

1. Pulmonary: TMP-SMX (1A) (TMP-SMX 15 mg/kg in 3-4 divided doses, for 6 to12 months)
2. Disseminated or CNS, Critically Ill: Imipenem plus TMP-SMX or Amikacin (2A)
3. Alternative: Linezolid, Meropenem (1A)

Multidrug-resistant (MDR) Infections in SOT Recipients

Evidence Statement

Carbapenems are effective for treatment of ESBL-producing *Enterobacter*iaceae. For Carbapenem-resistant *Enterobacter*iaceae (CRE), preferred antibiotics are ceftazidime/avibactam is preferred, whereas and ceftazidime/avibactam plus aztreonam or cefiderocol monotherapy are useful in metallo-β-lactamase producing CRE. Tigecycline is useful in treatment of CRE infections outside the urinary tract, and in absence of bacteremia, as combination therapy. For MDR *pseudomonas*, effective drugs are antipseudomonal β-lactam or Ceftolozane/tazobactam or Ceftazidime/avibactam. For carbapenem resistant acinetobcacter,high dose ampicillin-sulbactam, tetracycline derivatives (minocycline/ tigecycline), polymyxin B, or cefiderocol are options for combination therapy. For MDR *Stenotrophomonas maltophilia*, combination therapy with two agents (TMP- SMX, minocycline/ tigecycline, cefiderocol, or levofloxacin) is effective. However, critically ill patients can be treated with ceftazidime-avibactam plus aztreonam. For MRSA, vancomycin with therapeutic drug monitoring has most evidence. Linezolid can be used for skin and soft tissue infection (SSTI) and nosocomial *pneumoniae*. Teicoplanin is another efficacious alternative.

Recommendation

Empiric antibiotics for MDR pathogens should be chosen to cover the suspected pathogen spectrum and local microbiology (2A).

The Human Immunodeficiency Virus (HIV)-positive Patient in the Intensive Care Unit

Evidence Statement

Respiratory failure is the most important cause of ICU admission among HIV patients. Causes of community-acquired *pneumoniae* are similar to non-HIV patients. However, tuberculosis, and opportunistic infections (like *Pneumocystis Jirovecii*, *cryptococcus*, CMV) are also common, and can present with respiratory failure. Viral infections like influenza and covid-19 are other important causes. Increasing age, comorbidities, severity of illness, extent of organ dysfunction and cART naivety are predictors of increased mortality.

Recommendation

- Patients with severe *pneumoniae* who require intensive care and without risk of *Pseudomonas aeruginosa* should be empirically treated with an IV β-lactam plus IV macrolide (2A). Preferred β-lactams are ceftriaxone, cefotaxime, or amoxicillin-clavulanic acid. In patients who are allergic to penicillin, aztreonam plus azithromycin should be used (3A).
- If patients with HIV/AIDS develop acute respiratory failure and they have any of the risk factors (Table 1) for *Pseudomonas* infection we recommend dual antipseudomonal coverage such as anti-pseudomonal β-lactam plus aminoglycoside (examples of anti-pseudomonal β-lactams include ceftazidime, cefoperazone, cefoperazone-sulbactam, piperacillin-tazobactam, imipenem-cilastatin, or meropenem (3A).
- In patients who are allergic to penicillin, aztreonam can be used in place of the β-lactam. Combination therapy may be considered with the addition of aminoglycosides or antipseudomonal fluoroquinolones (e.g., levofloxacin, ciprofloxacin) (3A).
- We recommend continuing Azithromycin along with anti-pseudomonal therapy for coverage of atypical pathogens (2B).
- We recommend against using fluoroquinolones empirically to avoid development of drug-resistant TB. Patients should also undergo sputum testing for acid-fast *bacilli* simultaneously if fluoroquinolones are being used (3A).
- In patients who have risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) infection–empiric treatment should include vancomycin or linezolid (3A).
- Empiric therapy should cover *P. aeruginosa* or MRSA if previously isolated from sputum cultures (3A).
- Steroids are not indicated except in cases of refractory shock (2A).
- We suggest the addition of clindamycin (to vancomycin, but not to linezolid) in cases of severe necrotizing *pneumoniae* to minimize bacterial toxin production (3B).
- Those with CD4 counts <200/mm^3 and without signs of focal consolidation may be suspected to have PCP (2A).
- All diagnosed cases of HIV should receive cART and trimethoprim-sulfamethoxazole (TMP-SMX) for PCP prophylaxis to reduce the risk of *pneumoniae* (1A).
- A switch to oral therapy should be considered in patients with community-acquired *pneumoniae* (CAP) on IV antibiotic therapy who have improved clinically, can swallow, and tolerate oral medications, and have intact gastrointestinal function (2A).
- cART should be initiated promptly within 2 weeks of initiating therapy for the *pneumoniae* if not started (2A).
- Diagnostic work up of acute respiratory failure in HIV patient should consist of: (3A)
  - Complete blood count with CD4 cell count.
  - Sputum microscopy and culture especially for acid fast bacilli (AFB), Nucleic acid amplification tests (NAATs) for TB.
  - Chest imaging, lung ultrasound.
  - Bronchoalveolar lavage (BAL) for culture, staining with Gomori-Grocott or Giemsa or direct fluorescence antibody for PCP, PCR.

  - Blood culture.
  - BAL 1, 3 beta-D-glucan (BDG).
  - Urine antigen for *L. pneumophila* and *S. pneumoniae*.
  - Serum LDH, BDG.
- Rule out non-infectious causes of respiratory failure- COPD, Bronchiectasis, lung cancer, heart failure, lung fibrosis, interstitial pneumonitis, drug toxicity, asthma, pulmonary embolism (3A).

Hiv-positive Patient Presenting with Signs of CNS Infection in ICU

Evidence Statement

Patients with HIV and low CD4 counts are prone to opportunistic CNS infections like toxoplasmosis, tuberculosis, cryptococcosis. Less common opportunistic CNS infections are CMV, nocardiosis, aspergillosis, and neurosyphilis. CNS mass lesions and lymphoma are also common with low CD4 counts, Multiple etiologies can often co-exist. Clinical and laboratory evaluation and prompt management is associated with improved outcomes.

Immune reconstitution inflammatory syndrome (IRIS) is another differential if cART is started in undiagnosed or partially treated opportunistic infections.

cART should be continued in the HIV patients admitted to intensive care unit as much as possible.

Recommendation

- For a patient coming to ICU with altered CNS function and suspicion of meningitis, we recommend a third-generation cephalosporin- known to penetrate the blood-brain barrier - at higher doses, e.g., Ceftriaxone 2 gm BD intravenously (1A).
- We suggest the addition of vancomycin empirically to the initial treatment regime (1B).
- We recommend de-escalating antibiotics after culture reports are available (1A).
- In patients above 50 years of age, we suggest the use of additional ampicillin at high doses of 2 gm every 6th hourly (1B).
- In very young infants of age <1 month, we suggest Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside as the initial management (1B).
- Diagnostic work up for CNS infection in HIV patient should consist of: (3A)
  - Complete blood count with CD4 cell count.
  - Lumbar puncture, CSF (Cerebrospinal fluid) for cell count, glucose, protein, ADA (Adenosine deaminase), lactate, culture, PCR.
  - For immunocompromised host–*Toxoplasma gondi* IgG antigen and antibodies, cryptococcal antigen (serum and CSF).
  - Brain imaging preferably MRI (Magnetic resonance Imaging).

HIV-positive Patients Presenting with Suspected Bloodstream Infections or Sepsis of Unknown Origin

Evidence Statement

Lack of cART, low CD4 count, alcohol abuse, smoking, and comorbidities such as liver disease are risk factors associated with bacteremia in HIV patients. Common organisms seem to be non-typhoid Salmonellae, *Streptococcus pneumoniae*, *Escherichia coli*, *Staphylococcus aureus*, and coagulase-negative Staphylococci. Unidfferentiated fever in patients with low CD4 counts may be due to viral syndromes such as CMV, Disseminated *mycobacteria*l disease, disseminated fungal disease or noninfectious etiology. Disseminated opportunistic infections may trigger hemophagocytic lymphohistiocytosis. Drug-resistant organisms are also seen more commonly in HIV patients. Extensive diagnostic work up is needed in HIV patients with sepsis of unknown origin. In-hospital mortality in HIV patients depends on age, underlying comorbidities and extent of organ dysfunctions and not HIV related parameters such as viral load, CD4 cell count, admission for AIDS-related diagnoses, and prior cART use.

Recommendation

- In the presence of sepsis or septic shock, we recommend following the surviving sepsis guidelines like the management of other patients with sepsis (UPP).
- In the absence of septic shock or absence of risk factors for *Pseudomonas* a monotherapy with a third-generation cephalosporin or a cephalosporin, the b-lactamase inhibitor is sufficient (2A).
- In more severe disease states, such as in the presence of organ dysfunction or septic shock–a combination of broad-spectrum antibiotics may be used for initial empiric therapy (3A).
- Empiric gram-positive coverage is suggested for those who have risk factors for MRSA (UPP).
- Anti-fungal agents may be considered only if there is no clinical improvement or there is clinical deterioration even after 72 hours of appropriate empirical antibiotics therapy and CD4 counts $<200/mm^3$ (2A).
- We recommend against the use of routine empirical antifungal therapy (2A).

Congenital and Acquired Hyposplenism and Asplenia

What should be the Approach to Empiric Therapy in Patients with Hyposplenism or Asplenia who Develop Sepsis?

Evidence Statement

Patients with congenital and acquired hyposplenism/ asplenia are at high risk for encapsulated bacterial infections like *Neisseria meningitidis*, *Streptococcus pneumoniaee* and *Haemophilus influenzae* type b. These patients are more likely to have severe sepsis, and overwhelming post-splenectomy infection (OPSI). OPSI can present with flu-like illness at onset, and rapidly progress to septic shock and death, and therefore needs prompt institution of antibiotics covering for both gram-positive and gram-negative organisms under close observation in high dependency or intensive care units.

Recommendation

- If an asplenic or hyposplenic patient is suspected to have sepsis we recommend administration of IV ceftriaxone before transferring the patient to a higher center (2A).
- We recommend that all patients with Overwhelming Post-Splenectomy Infection (OPSI) be treated in the ICU (UPP).
- We recommend empiric antibiotic therapy for aslpenic patients with a combination of ceftriaxone and vancomycin (1A).
- In case of allergy to β-lactams, we recommend vancomycin with aztreonam or fluoroquinolones in adults. Do not delay administration of antibiotics, be prepared to treat reaction (UPP).
- We recommend to add clarithromycin or erythromycin in case of respiratory symptoms (3A).

- We recommend empiric therapy with IV Cefotaxime + vancomycin+ ampicillin, if the patient age <2 months (3A).
- All febrile asplenic patients should be screened for malaria with peripheral smears. Start artesunate based antimalarial therapy, if the history is suggestive of Malaria (UPP).
- If gram staining of peripheral blood smear shows gram-negative bacilli, we recommend addition of antipseudomonal coverage to the therapy (3A).
- We recommend that urine be checked for urinary antigen for *streptococcus pneumoniae*. (2A).
- We suggest RT-PCR test for simultaneous identification of 3 main encapsulated bacteria (*Str pneumoniae*, *H. influenzae* type B and *N. meningitidis*) (3B).
- We recommend that all asplenic patients should receive immunization against encapsulated bacteria (*S. pneumoniae*, *H. influenzae*, and *N. meningitidis*) (1A).
- Immunization against seasonal flu is recommended for patients over 6 months of age (1A).
- Vaccination programs should be started no sooner than 14 days after splenectomy (1A).
- If the patient is discharged before 15 days after splenectomy or angioembolization, where the risk to miss vaccination is deemed high, we suggest that patient be vaccinate before discharge (1B).
- Antibiotic prophylaxis is indicated in patients for 1-2 years after splenectomy and lifelong for patient had an episode of overwhelming infection or immunocompromised (2B).
- We recommend self-administration of one dose of, in stock "pill in pocket", prescribed antibiotics in the event of any sudden onset of unexplained fever, malaise, chills or other constitutional symptoms, when medical consultation not readily accessible within 2 hours (2A).
- We suggest that any patient with sepsis having risk factor for hyposplenia, the peripheral smear should be checked for Howell-Jolly bodies. (2B)
- We recommend formulation of Spleen registry. (UPP).

Patients with Primary Immune Deficiency in the ICU

Evidence Statement

A diagnosis of primary immunodeficiency should be considered in patients with serious infections. Significant family history, hematologic abnormalities like neutropenia, lymphopenia, recurrent infections, or infections with uncommon organisms can lead to evaluation for primary immunodeficiency. Recurrent sinopulmonary infections are seen with humoral immuno-deficiencies. Recurrent infections with organisms like tuberculosis or endemic fungi should lead to evaluation for cell mediated immunodeficiency. Microbiologic diagnosis is important in patients with suspected immunodeficiency due to higher incidence of co-infections and drug resistant infections. In patients with primary immunodeficiency with serious infections, empiric coverage for causative organisms, including viruses and invasive fungal infections is practiced. Treatment for underlying immunodeficiency (e.g., intravenous immunoglobulin therapy) and comorbid autoimmune conditions improves outcomes.

Recommendations

- PID should be suspected when the following history/symptoms or signs are present: (UPP).
  - Family history of sibling death.
  - Four or more ear infections within 1 year.
  - Two or more serious sinus infections or *pneumoniae*s within 1 year.
  - Two or more months on antibiotics with little effect.
  - Two or more deep seated infections including septicemia.
  - Persistent thrush in mouth or fungal infection on skin.
  - Infections in multiple anatomic locations.
  - Increasing frequency and severity of infections with age.
  - Recurrent serious infections with common pathogens.
  - Serious infections with unusual pathogens.
- We recommend that when PID is suspected, HIV infection should also be considered, and testing should be performed for HIV (UPP).
  - We recommend that patient should be investigated for PID when: (3A).
  - In neonates, Absolute lymphocyte count (ALC) of <2000/mm^3 in cord blood or in an infant an ALC of <4000/mm^3.
  - Severe hypogammaglobulinemia with IgG <1 50 mg/dL.
  - Absolute lymphocyte count <4000/mm^3 (In non-chemotherapy setting).
  - Unusual organism picked up on microbiology.
  - Unexplained neutropenia.
- We recommend that Initial laboratory screening should include a complete blood count with differential counts (including Absolute Lymphocyte Count, Absolute Neutrophil Count, Absolute Monocyte Count) and measurement of serum immunoglobulin and complement levels (UPP).
- We recommend Severe Combined Immune deficiency (SCID) be considered as a pediatric emergency and attention be paid to Absolute Lymphocyte Count, at all time in ICU. If the Absolute Lymphocyte Count is less than normal for the age, we recommend to take immunology reference, use irradiated blood products, and avoid live vaccines till diagnosis is confirmed or ruled out (UPP).
- We recommend that patient be investigated for Combined Variable Immuno-deficiency (CVID) when patient has any of the following: (UPP)
  - Recurrent bacterial infections.
  - Serum IgG, IgM, IgA levels (at least two of the three) with a marked decrease (at least 2 SD below the mean for age).
  - Onset of immunodeficiency at more than 2 years of age.
  - Absence of isohemagglutinins and or poor response to vaccines.
- We recommend that immunology consult be obtained for these patients and the patient be investigated to diagnose specific form of immunodeficiency (UPP)
  - Lymphocyte subpopulations by Flow cytometry (CD3, CD4, CD8, CD19, CD20, CD16 & CD56).
  - Naive T cells, Memory B cells, Memory T cells.
  - T-cell response to mitogens.
  - Nitroblue Tetrazolium-NBT test.
  - Complement levels.
  - Bone Marrow and Genetic tests.
- We recommend for all critically ill patients with suspicion of PID the empirical antimicrobial treatment with IV Carbapenems with IV Vancomycin/Teicoplanin for broad-spectrum coverage. (UPP, A). Voriconazole is the preferred antifungal in case of proven, possible or probable invasive fungal infection with *aspergillus* (IA).
- In critically ill patients diagnosed with Combined B and T cell deficiency the antimicrobial drug of choice is IV

Carbapenems with Vancomycin/Teicoplanin and Trimethoprim-Sulfamethoxazole (UPP).
- In critically ill patients diagnosed with Combined B and T cell deficiency with suspicion of viral infections, we recommend: (UPP)
  - IV Acyclovir if herpes group of infection is suspected.
  - Oral oseltamivir if Influenza virus is suspected.
  - IV Ganciclovir if CMV is suspected radiologically or by laboratory tests.
- In critically ill patients diagnosed with B cell deficiency, based on the organisms expected (Capsulated), we recommend IV ceftriaxone with IV Vancomycin/ Teicoplanin (UPP).
- We recommend IV Immunoglobulin (IVIg) at dose of 1 gm/kg weekly in cases of severe infections especially ECHO /Enterovirus / Polio virus induced encephalitis (UPP).
- In critically ill patients diagnosed with Phagocyte disorder we recommend.
- Antimicrobial drug of choice to be IV Carbapenems with IV Vancomycin/ Teicoplanin and Voriconazole (UPP).
- We recommend the use of Granulocyte colony stimulating factor (GCSF) in patients of congenital Neutropenia (UPP).
- In critically ill patients diagnosed with complement deficiency the antimicrobial drug of choice is IV Cephalosporin (UPP).
- We recommend appropriate cultures, and PCRs; for organisms likely to cause infections pertinent to the conditions they are suffering from (UPP).
- Attempt should be made to identify the microorganisms directly or on PCRs as serological tests in infectious diseases could give false-negative results if there is an antibody defect (UPP).
- We recommend the use of Multiplex PCR to help diagnose infections (UPP).
- We recommend intravenous Immunoglobulin for treatment of all antibody deficiency diseases, at doses of 400 mg/kg/doses every 4 weekly. We recommend 2 gm/kg single dose (Severe Infections) or 1 gm/kg weekly till infection subsides (UPP).
- We recommend to maintain serum IgG trough levels above 500 mg/dL and above 700 mg/dL in bronchiectasis (3A).
- We recommend thoracic computed axial tomography, lung function tests with spirometry and DLCO every 6 months after discharge (UPP).
- We recommend hematopoietic stem cell transplantation in cellular and macrophage immunodeficiency (UPP).
- We recommend monoclonal antibodies such as rituximab only in autoimmune complications related to CVID (UPP).
- We recommend Rituximab be given in PID complicated with EBV viremia (UPP).

What should be the Approach to Vaccinations and Antimicrobial Prophylaxis at Discharge for Patients with Primary Immunodeficiency Requiring Intensive Care?

Evidence Statement

Live vaccines are contraindicated in SCID whereas all vaccines are safe and effective in complement deficiency. Antifungal prophylaxis and PCP prophylaxis are important to prevent invasive life-threatening infections in patients with PID.

Recommendations

- All forms of live vaccines, viral and bacterial, are contraindicated in patients with SCID (UPP).
- We recommend vaccination for diagnosed patients with complement deficiency at time of discharge (UPP).
- We recommend avoiding BCG vaccination in Chronic Granulomatous Disease /MSMD patient (UPP).
- We recommend antifungal and anti PCP prophylaxis for all patients diagnosed with PID shifted from ICU (UPP).
- PID patients with chronic granulomatous disease should be treated with Itraconazole (IA) and Trimethoprim-Sulfamethoxazole (2A).
- PCP prophylaxis should be given to all patients with Combined B and T or T cell deficiency with drug of choice being Trimethoprim-Sulfamethoxazole (1A).
- We recommend antifungal prophylaxis in all patients with T cell defects (3A).

Introduction

Severe infections are common indications requiring admission to intensive care units (ICU). For these patients, effective antibiotic therapy is lifesaving. The resistance to currently available antibiotics has increased over the last few years. Secondly, only a few new antibiotics have been marketed over the last few years and will be available in the coming years. Another issue is the ever-increasing number of admissions of immunocompromised patients in the intensive care units due to the availability of effective treatment options for acquired immunodeficiency states and cancer, resulting in prolonged survival and cure, use of multiple lines of myelosuppressive therapies at diagnosis and relapse, and better outcomes in these patients. The best way to preserve the efficacy of existing antibiotics is to use these drugs appropriately. One way to do this may be to increase awareness and develop guidelines for the prescription of antibiotics. International guidelines on antibiotic prescription in ICUs have been framed. The Indian Society of Critical Care Medicine also formulated guidelines for empiric antibiotics in intensive care units and immunocompromised patients. [1,2] Regular updation of guidelines is important with arrival of new research and evidence.

Scope of the Guidelines

The scope of these guidelines includes antibiotic prescription for common bacterial infections for *pneumoniae* (community-acquired, hospital-acquired and ventilator-associated), bloodstream infections, abdominal infection (hepato-biliary, pancreatic, urogenital), central nervous system, skin and soft tissue infections in patients admitted in ICU. These guidelines also include recommendations for use of empiric antimicrobials in immunocompromised patients.

Methodology

This document is the latest effort to improve existing antibiotic prescription guidelines in the intensive care unit (ICU) and antimicrobial prescription guidelines in critically ill immunocompromised patients under the aegis of Indian Society of Critical Care Medicine.[1,2] The committee was composed of experts from various fields specializing in ICU infections and was divided into five groups. The team updated the evidence by extensively reviewing the literature through various electronic databases, including PubMed and Embase. The team also reviewed cross-references from articles and all major international guidelines on the topic. The experts in each group exchanged and reviewed relevant literature, and consensus was reached on the scope and questions

Table 1: Criteria for level of evidence and grading of strength of recommendations used in formulation of current guidelines

Quality of evidence	*Level*
Evidence from ≥1 good quality and well conducted randomized control trial(s) or meta-analysis of RCT's.	1
Evidence from at least 1 RCT of moderate quality, or well-designed clinical trial without randomization; or from cohort or case-controlled studies.	2
Evidence from descriptive studies, reports of expert committees, or opinions respected authorities based on clinical experience.	3
Not backed by sufficient evidence; however, a consensus reached by the working group based on clinical experience and expertise.	Useful practice point (UPP)
Strength of Recommendation	*Grade*
Strong recommendation to do (or not to do) where the benefits clearly outweigh the risk (or vice versa) for most, if not all patients.	A
Weak recommendation, where benefits and risk are more closely balanced or are more uncertain.	B

that needed to be addressed in formulating the guidelines. After thorough discussions and review, the guidelines were framed to ensure their reliability and relevance in clinical practice. Modified Grade System was utilized to classify the quality of evidence and the strength of recommendations (Table 1). Draft document thus formulated was reviewed by all committee members; comments and suggestions were incorporated after discussion, and a final document was prepared. The final document was reviewed and accepted by all expert committee members.

Pharmacokinetics and Pharmacodynamics

Pharmacokinetics deals with the time course of drug absorption, distribution, metabolism, and excretion while pharmacodynamics involves relationship between drug concentration and its effects including toxicity. Each antibiotic has its own pharmacokinetic profile though each class of antibiotics has its class specific properties as well. Each class of antimicrobials has a different pharmacodynamic profile based on different inhibitory characteristics on bacteria.

Individualized dosing regimens using known pharmacokinetics and pharmacodynamic characteristics are important to optimize patient outcomes and minimize antimicrobial resistance. Pharmacokinetic profiles change over time in critically ill patients, warranting periodic reconsideration of dosing regimens.

The factors determining metabolism and effects of an antibiotic include basic antibiotic characteristics such as lipophilic or hydrophilic, patient status such as volume status and end organ function and changes in pathophysiologic characteristics i.e., systemic inflammation and hemodynamics. Hydrophilic antibiotics have low volume of distribution, predominantly renal clearance and low intracellular penetration as compared to lipophilic antibiotics. Examples of hydrophilic antibiotics include beta-lactams, aminoglycosides, vancomycin, linezolid and colistin while lipophilic antibiotics are fluoroquinolones, macrolides, clindamycin and tigecycline.[3]

The antibiotics can be broadly classified into those with concentration dependent killing activity and those with time dependent killing activity. The examples of former include aminoglycosides, fluoroquinolones, metronidazole, colistin and clindamycin whereas that of latter include beta-lactams, linezolid and tetracyclines.

Sepsis affects the drug metabolism by various mechanisms. Being a hyperdynamic state it (pharmacologically or pathophysiologically enhanced) can increase creatinine clearance and hepatic perfusion thus increasing drug removal. At the same time, sepsis induced organ-dysfunction can reduce metabolism and elimination of active drug. Renal replacement therapies can increase clearance for some drugs like piperacillin-tazobactam and meropenem. Body has adaptive methods for increasing drug clearance during states of multiorgan failure. For example, gastrointestinal clearance of ciprofloxacin is increased in renal failure while biliary clearance of piperacillin increases in renal failure. Serum protein concentration also affects the antibiotic concentration. Significant changes in free fractions of drug are only relevant for highly protein bound drugs (>95%). Small changes in protein binding result in huge relative changes in free (unbound) drug. Changes in protein binding will affect both clearance as well as volume of distribution. Most antibiotics have low protein binding (<90%) except ceftriaxone (95% bound to albumin), ertapenem, teicoplanin, aztreonam and daptomycin.

An open-label RCT involving 140 patients with sepsis compared continuous infusion of beta-lactams with intermittent infusion and demonstrated higher clinical cure rates and higher ventilator-free days in continuous infusion group without any mortality difference between two groups.[4] Similar results have been found in various other studies as well though a double-blind study by Dulhunty et al. did not find any difference in ICU-free days, 90-day survival and clinical cure between continuous infusion and intermittent infusion groups.[5] An individual patient data meta-analysis found significantly lower hospital mortality rates with continuous infusion of beta-lactams as compared to intermittent infusion in patients with severe sepsis.[6] Prolonged infusion (>3 hours) of antipseudomonal beta-lactams was associated with lower all-cause mortality than short-term infusion (<60 minutes) in a meta-analysis of 22 studies comprising 1876 patients with sepsis (Risk ratio, RR 0·70, 95% CI, 0·56-0·87).[7] Regarding vancomycin, a meta-analysis including 11 studies comparing continuous versus intermittent infusion found that patients treated with continuous infusion had a significantly lower incidence of nephrotoxicity without any difference in treatment failure and mortality.[8]

Evidence Statement

Time-dependent antibiotics require drug concentrations greater than the minimum inhibitory concentration (MIC) for a certain time period between doses, which usually ranges from 40 to 50% of inter-dose interval for their best action. Continuous infusions are preferred over extended infusions for beta-lactam antibiotics and are associated with clinical benefits like decrease in hospital stay, cost of therapy and mortality. For vancomycin, continuous infusion is associated with reduced toxicity and cost of therapy but no mortality benefit.

Newer Diagnostics Including Multiplex PCR

Respiratory tract infections (RTIs) are amongst the most common infections in ICUs with high morbidity and mortality rates reported worldwide.[9,10] A wide variety of agents, including bacteria, viruses, and fungi are responsible for causing RTIs, which are subclassified as upper respiratory infections (URTIs) and lower

respiratory infections (LRTIs).[11,12] Viruses followed by bacteria, are the most common cause of RTIs, although *mycobacteria*l and fungal pathogens can cause them as well.[11] Syndromic diagnosis is the most used strategy for clinical management because a careful evaluation by trained physician backed by radiological imaging and laboratory based biomarkers, is rapid, inexpensive, and easy to implement.[13,14] However, syndromic approach fails to establish the definite etiological diagnosis. At present there is a great deficit in establishing the etiologic diagnosis of RTIs; in most studies almost 30-60% of cases remain without an etiologic diagnosis.[14–17] Pathogen-specific microbiological diagnostic test can be categorized into direct diagnosis (microscopic examination, cultures, antigen detection and molecular detection) and indirect diagnosis (antibody detection by serological tests).[14,16] Despite being the gold-standard, microbiological diagnosis cannot rely on conventional culture methods alone. These methods have low diagnostic yields due to various host factors, severity and extent of *pneumoniae*, use of empirical antimicrobials, and sampling method used (quality and site of specimens, transportation conditions, etc.). In addition, for pathogens such as *Mycobacterium tuberculosis*, atypical organisms like *Legionella, Chlamydia pneumoniaee, Mycoplasma pneumoniaee,* fungi, and viruses; culture has either a low sensitivity and/or is time-consuming.[16,17]

Recent times have seen a surge in rapid culture-independent novel assays and molecular diagnostics for common respiratory pathogens, as well as the availability of updated tests for newer strains of pathogens. These include antigen detection assays, reverse transcription–quantitative polymerase chain reaction (RT-qPCR) testing, multiplex PCR panels targeting multiple organisms, plasma cell-free DNA, next-generation sequencing (NGS), etc. on blood, and upper and lower respiratory tract specimens to detect *viral, bacterial, fungal, and mycobacterial infections*.[11,18–21] These have enabled major advances in the speed and sensitivity of diagnostics for RTIs, although the clinical utility of these methods is still under evaluation. However, the clinical implementation of these techniques is challenging as mere detection of pathogens in respiratory specimens does not necessarily imply acute infection. [14,16] The increased sensitivity for detection of pathogens poses problem of distinctions between pathogens, colonizers, commensals, and contaminants. Other challenges include detection characteristics, bioinformatics requirements, and reimbursement issues. [16,20,21]

The disease prevalence (i.e., the pretest probability of a given pathogen) is integral to diagnostic decision making since it affects the positive- and negative-predictive values of these assays. [14,16,20]

Routine viral testing for influenza by molecular methods in general adult population with RTIs is not recommended, especially in periods of low prevalence. However, for more serious cases, such as those requiring hospitalization, ICU care or therapy, or *pneumoniae* in pediatric patients or immunocompromised hosts (ICHs), rapid diagnosis can be important.[19,22–25]

Rapid molecular diagnostics for viral, bacterial, and fungal pathogens should be considered in carefully selected cases symptomatic cases with worsening or new radiological infiltrates, having moderate/ severe illness requiring hospitalization/ICU care; pediatric or ICH population, and/or in cases suspected to have polymicrobial/multidrug-resistant infections.[14,16] NAATs (nucleic acid amplification tests) for the detection of respiratory pathogens have been available since early 2000s. These tests differ in complexity (i.e., PCR, nucleic acid sequence-based amplification (NASBA), transcription-mediated amplification (TMA), strand displacement amplification (SDA), loop-mediated isothermal amplification (LAMP), rolling circle amplification (RCA), and others) and, pathogen coverage.[12,26,27] Moreover, the accuracy is not only dependent on their specific chemistry, but also critically affected by the type, quantity, and quality of specimens collected.[26,28] There are a number of NAATs available commercially for the detection of respiratory pathogens, many of which are FDA approved. Simple to complex sample-to-answer molecular platforms and panels are available, which can be subclassified as low-plex integrated test systems (targeting 1-4 pathogens per assay, allow random access), moderate complexity multiplex integrated systems (moderate sample throughput i.e. 1-12 samples/run, with a fast turnaround time (TAT) of 1-2 hours, and allowing random/batched access), and high complexity multiplex panel assays (high sample throughput i.e. more than 20/run, usually batched access, with higher TAT). Syndromic multiplex panels require considerable knowledge, training, and experience. Despite the advantages, implementation of high throughput panels can be challenging because of demanding sample preparation, processing, and result interpretation procedures, and the turnaround time varies from approximately 5–16 h.[26,28] NAAT based point-of-care (POC) testing is relatively new in the realm of RTI diagnosis, with contradicting opinions regarding their implementation and clinical utility. These have extremely short turnaround times (<30 min), minimal hands-on time (1–2 min), and can be easily operated by non-laboratory staff members, thereby making them suitable for near patient implementation and testing. However, these can be costly and more prone to incorrect results and contamination due to laboratory handling by inexperienced personnels.[26,27,29] These have been summarized in Table 2.

There are upcoming technologies like untargeted next-generation sequencing-based metagenomics (mNGS) testing for accurate and unbiased detection of expected or unexpected pathogens that are either not targeted by the panel or missed due to highly divergent genome sequences. However, diagnostic implementation of NGS is currently limited by incomplete understanding of analytical performance, high cost of the system and complexity of sequence data analysis.

Currently, molecular diagnostics is the gold standard for the diagnosis of viral respiratory infections.[15–17] Several types of specimens can be used for detection of respiratory viruses, including: bronchoalveolar lavage (BAL), throat/oropharyngeal (OP) swab, nasopharyngeal (NP) washes, NP aspirates, lung aspirates, and NP swabs, although the appropriate specimen type depends on the specific patient population.[26,27,29] However, false-positive or false negative results can be a problem due to poor handling of specimen.[12,15] In a recent meta-analysis, the pooled sensitivity and specificity of rapid viral NAAT were 90.9% and 96.1%, respectively, for the detection of either influenza virus, respiratory syncytial virus (RSV), influenza virus and RSV, or a viral panel including influenza virus and RSV.[27] Upfront multiplex testing for multiple viruses may be most cost-effective in certain specific populations such as pediatric patients, ICH population, and critically ill patients with *pneumoniae* where it can reduce unnecessary antibiotics as well as chest radiographs.[16,23] A recent meta-analysis compared the diagnostic accuracy of Luminex NxTAG respiratory pathogen panels (RPPs)™ (index) against other RPPs (comparator) for detection of RSV and influenza viruses.[30] For RSV, predicted sensitivity was 99% and specificity 100%. For influenza A and B, predicted sensitivity was

Table 2: Types of FDA-approved commercially available molecular panels for bacterial and viral RTIs

Diagnostic assay	*Type of respiratory specimen*	*Turn-around time*
Influenza A/B only		
a) Waived POCT	Nasal/Nasopharyngeal swab	15–30 minutes
b) Moderate to high complexity assays	Nasal/Nasopharyngeal swab	30 minutes – 2 hours
RSV only	Nasal/Nasopharyngeal swab	15–30 minutes
Influenza A/B plus RSV		
a) Waived POCT	Nasal/Nasopharyngeal swab	15–30 minutes
b) Moderate to high complexity assays	Nasal/Nasopharyngeal swab/ Nasopharyngeal aspirates/Nasal washings	1–3 hours
Parainfluenza viruses	Nasopharyngeal swab	2–4 hours
Multiple viruses plus atypical bacteria		
a) Waived POCT	Nasopharyngeal swab	1–2 hours
b) Moderate to high complexity assays	Nasopharyngeal swab/ Nasopharyngeal aspirates/Nasal washings	1–5 hours
Multiple viruses (Moderate to high complexity assays)	Nasopharyngeal swab/ Nasopharyngeal aspirates/Nasal washings/ Bronchoalveolar lavage (BAL)	2–5 hours
Multiple bacteria with resistance genes (Moderate to high complexity assays)	Endotracheal aspirates/ BAL	4–5 hours
Multiple viruses and bacteria with resistance genes		
a) Waived POCT	Sputum/Endotracheal aspirates/ BAL	1–2 hours
b) Moderate to high complexity assays	Sputum/Endotracheal aspirates/ BAL	>6 hours

Adapted from: Murdoch DR, Werno AM, Jennings LC. Microbiological Diagnosis of Respiratory Illness: Recent Advances. In Kendig's Disorders of the Respiratory Tract in Children; Elsevier: Amsterdam, The Netherlands, 2019; pp. 396–405.e3. Hanson KE, Azar MM, Banerjee R, et al. Molecular Testing for Acute Respiratory Tract Infections: Clinical and Diagnostic Recommendations From the IDSA's Diagnostics Committee. Clin Infect Dis. 2020 Dec 17;71(10):2744-2751

97% and 98% respectively; specificity 100% and 100%, respectively. Multiplex vial panel can increase the detection of a number of infections that otherwise go undiagnosed because they are not suspected. A recent study demonstrated a 75% higher recovery rate of unexpected *M. pneumoniae*e infection using multiple PCR.[28] NAAT based POC assays are currently limited to the detection of influenza A/B and RSV viruses, with the exception of the FilmArrayR RP EZ (BioFire) which detects 14 targets. The clinical performance of these assays is reported with a high sensitivity (87–100%) and specificity (>98%) for detecting influenza A/B and RSV in pediatric and adult patients. However, the clinical performance varies, and sensitivity is significantly low for influenza B (45.2–54.5%).[26]

NAAT based PCR assays have been developed for numerous bacterial pathogens, with greater accuracy and sensitivity of identification compared to conventional culture-based diagnostics.[12,31,32] NAAT platforms may allow co-detection of multiple bacteria, viruses, or bacteria plus viruses in up to 30–40% of cases and have important implications for hospital infection control and treatment decisions.[31,32] High analytic sensitivity of multiplex panels also translates to high negative predictive values (i.e., generally >97%, depending on prevalence), but there may be important differences among individual panel targets or across manufacturers.[15–17,32,33] Due to the need for isolation of the microorganism for antibiotic susceptibility testing, molecular methods can theoretically replace cultures only in cases in which the pathogens are of predictable susceptibility or the genetics of resistance are well defined.[34] Furthermore, there can be inconsistencies with resistance gene detection, especially in cases of co-infections or when the sample is obtained from an anatomical site with low prevalence of resistant pathogens.[32–36] For example, the CTX-M type extended-spectrum beta-lactamases gene was reported for any member of the families *Enterobacter*iaceae, *Acinetobacter* spp., or *P. aeruginosa*, and for this reason, when a resistance phenomenon is common to different bacteria, the conventional culture and the phenotypic AST are required to confirm the indication of the resistance marker.[32]

Fungal diagnostics are rapidly evolving as conventional culture tests are faced by many challenges such as poor sensitivity, slow TATs, laborious process, and invasive nature of specimens required for testing. [19,37] Serological testing represents a quicker way of detecting the causal fungi, aiding in the diagnostic decision-making process.[38] The major limitation of antibody-based testing is seen in ICH population, who are unable to elicit adequate levels of antibodies and may show false negative results.[37,38] Galactomannan (GM) and β-1,3-D glucan (BDG) are fungal cellular wall constituents that can be detected in serum or bronchoalveolar lavage (BAL) fluid to aid in the diagnosis. GM is more specific to *Aspergillus* spp. than BDG. In a recent meta-analysis, serum GM in ICHs suspected of IPA had a pooled sensitivity and specificity of 71%, and 89% respectively.[39] BAL GM, on the other hand, had a pooled sensitivity and specificity of 84%, and 88% respectively. BDG is pan-fungal antigen found in *Candida* spp., *Aspergillus* spp., Mucorales, and *Pneumocystis jirovecii*, etc. Antigen and antibody testing have made great strides with introduction of newer techniques like lateral flow assay (LFA) based tests to allow higher diagnostic accuracy; however, cross-reactivity with other fungi, and test availability remain considerable issues.[38,39]

Fungus-specific quantitative real-time PCR amplification has been available for diagnosis of invasive fungal infections.[37] In the recent meta-analysis, the serum or whole-blood fungal PCR had pooled sensitivity and specificity of 81%, and 79% respectively. BAL fungal PCR in the same group had pooled sensitivity and specificity of 90%, and 96% respectively.[39]

Early and accurate diagnosis of causative pathogens in RTIs can help in administering appropriate antimicrobial therapy (time to initiation, duration, and discontinuation), initiate effective infection control measures, and reduce length of hospital/ICU stay.[40–42] Rapid molecular testing for influenza can decrease unnecessary antibiotic use, improve antiviral prescribing, limit ancillary testing, shorten lengths of stay, and promote infection-control practices.[22–25] Several studies evaluated the clinical and economic impacts of multiplex respiratory testing, and concluded that, despite their high cost, multiplex panels offering custom orders can limit unnecessary testing, improvement in the clinical outcomes of patients mainly by the early administration of a targeted antibiotic therapy, and in the rapid adjustment and de-escalation of empirical therapy resulting in a short duration of treatment, minimizing patient costs. Current evidence suggests that syndromic multiplex PCR testing, coupled with antimicrobial stewardship, increases the timeliness of antiviral prescription in influenza patients and the rapid appropriateness of antibiotic treatment.

Rapid pathogen identification tools for UTIs utilize existing molecular platforms such as mass spectrometry and multiplex PCR. MALDI-TOF (matrix-assisted laser desorption ionization time of flight) mass spectrometers are increasingly used for unambiguous species-level identification of bacteria and yeast.[43,44] Multiplex PCR offers a cost-effective and rapid approach to pathogen identification. Many studies have examined PCR assays for specific UTI pathogens. All such studies have found that multiplex PCR compares favorably with a standard urine culture.[45–47] A recent meta-analysis, concluded that multiplex PCR and RT-PCR are molecular techniques that might be comparable to standard urine culture for UTI diagnosis, with a pooled sensitivity at 80% and a specificity at 83% for multiplex-PCR.[48] Upcoming molecular diagnostics include the Next-generation sequencing (NGS) studies. Next-generation sequencing (NGS) has been used to identify causative pathogens in various infectious diseases including UTI.[49] A systematic review compared the diagnostic and therapeutic values of molecular diagnostic methods (NGS, and PCR) to urine culture in the management of UTI in adults.[50]

Nucleic acid purification directly from the fecal samples is a first and key step for rapid molecular diagnosis of enteric viruses.[51,52] Multiplex RT-qPCR assay have been developed for the detection of different enteric viruses, namely Astrovirus, Adenovirus, Rotavirus A, C, Sapovirus, and Enterovirus from stool samples; many assays being able to detect up to 19 enteric pathogens with high sensitivity.[53] A recent pragmatic, open label, randomized controlled trial (RCT)[54] studied the clinical impact of syndromic molecular testing (mPOCT) for gastrointestinal pathogens in 128 adult patients presenting to hospital with suspected gastroenteritis. They found that 65% of patients received antibiotics in m-POCT group versus 47% in the control group ($p = 0{\cdot}0028$). Another recent prospective, single-center, RCT also found that use of multiplex GI PCR led to an increase in antibiotic use for bacterial and protozoal causes of infectious diarrhea compared to usual testing.[55]

Community-acquired *Pneumoniae* in the Intensive Care Unit

Community-acquired *pneumoniae* (CAP) refers to symptoms suggestive of acute lower respiratory tract illness (cough with or without expectoration, dyspnea, pleuritic chest pain) along with systemic manifestations (fever, chills, rigors or severe malaise), clinicoradiologic evidence (like crepitations or bronchial breath sounds; lobar or patchy consolidation or interstitial infiltrates) and no other explanation for the illness.[56,57] CAP can simply be defined as *pneumoniae* which is not acquired in hospital or long-term care facility.[58]

What are the Common Organisms Causing Community-acquired *Pneumoniae* in Intensive Care Unit Worldwide and in India?

Most common etiology of community-acquired *pneumoniae* are viruses, ranging from 8.6% to 56.2%.[59] Pooled proportion of viral *pneumoniae* was 25.5% (95% CI, 22–29%) amongst patients requiring admission, and 29% (95% CI, 14.5–43.4%) in patients requiring ICU admission. Most common viruses responsible for CAP were influenza (8%; 95% CI, 6.3–9.6%), rhinovirus (5.7%; 95% CI, 4.3–7.1%), respiratory syncytial virus (2.2%; 95% CI, 1.6–2.8%) and coronavirus (3.3%; 95% CI, 2.3–4.2%).[59] Common organisms causing CAP requiring intensive care admission worldwide include *streptococcus pneumoniaee* (12–43%), *Haemophilus influenzae* (0–12%), *Legionella pneumophila* (0–30%), *Staphylococcus aureus* (0–19%), gram-negative enteric bacilli (0–27%), *Mycoplasma pneumoniaee* (0–7%), *chlamydia* species (0–2%) and *Coxiella burnetti* (0–2%).[60] In a recent active population-based surveillance study, *streptococcus pneumoniaee*, *Staphylococcus aureus* and *enterobacter*iaceae were more commonly implicated in CAP requiring intensive care ($p < 0.001$).[61] In secondary analysis of an international, multicenter, point-prevalence study on CAP in ICU, bacterial etiology could be identified in 35.3% patients. *Streptococcus pneumoniaee* (8.2%), *Pseudomonas aeruginosa* (4.1%), *Klebsiella pneumoniaee* (3.4%) and methicillin resistant *Staphylococcus aureus*, i.e., MRSA (3.0%) were the most common organisms isolated. MRSA and *pseudomonas* caused higher proportion of ICU admissions ($p < 0.01$).[62] MRSA has been identified as important cause of CAP in intensive care unit (ICU) settings in earlier observational studies, case series and case reports.[63–66] MRSA *pneumoniae*.

Literature on epidemiology of CAP in India comes from hospital based observational studies and surveillance data as the ICU specific studies are not available. *Streptococcus pneumoniaee* (2–35.8%), *Mycoplasma pneumoniaee* (3–24%), *chlamydia pneumoniaee* (6–18%), *Legionella* spp. (2–15%), *Mycobacterium tuberculosis* (0–5%), *Haemophilus influenzae* (0–15.4%), *Staphylococcus aureus* (2–13%), *klebsiella pneumoniaee* (3–25.5%), other gram-negative bacilli (0–19%) are the common organisms implicated in CAP requiring hospitalization in India.[67–89] High prevalence of *Staphylococcus aureus* (26.7%) and MRSA causing CAP (60.9% of staphylococci) has been reported in one Indian study.[68]

Increasing age, active smoking, chronic obstructive pulmonary disease (COPD) and diabetes mellitus appear to be significant risk factors for development of severe CAP. Structural lung disease and COPD are risk factors for infection due to *Pseudomonas aeruginosa*.[56,90–92]

Streptococcus pneumoniaee largely remains sensitive to amoxycillin-clavulanic acid and azithromycin with only few studies reporting resistance to amoxycillin-clavulanic acid (20%), levofloxacin (20%) and azithromycin (13%).[56,76,77,86] There is limited data on antibiotic sensitivity patterns of other microbes. *H. influenzae* also seems to be largely sensitive to amoxycillin clavulanic acid and azithromycin; in one study, 23% isolates were resistant to amoxycillin-clavulanic acid, 13% were resistant to azithromycin whereas only 6% were resistant to cefuroxime.[86] gram-negative bacilli (GNB) are usually sensitive to beta-lactams

and fluoroquinolones.[84] However, in recent studies, prevalence of extended spectrum β-lactamase (ESBL) organisms appears to be increasing with resistance to carbapenems (16.6%), piperacillin-tazobactam (39.5%), and cefoperazone-sulbactam (42%) reported in a recent prospective study.[86] Drugs effective against methicillin sensitive *Staphylococcus aureus* (MSSA) include penicillinase resistant penicillins (nafcillin, oxacillin) or penicillin-beta-lactamase combination (amoxycillin-clavulanate, ampicillin-sulbactam). Community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA) has sensitivity to tetracycline, doxycycline, minocycline, -tigecycline, clindamycin and co-trimoxazole, whereas hospital-acquired MRSA (HA-MRSA) is sensitive to vancomycin, teicoplanin, daptomycin, linezolid and ceftaroline.[93–97] Linezolid has shown better clinical success rate as compared to vancomycin in MRSA *pneumoniae* (57.6% vs 46.6%; 95% CI, for difference 0.5%-21.6%; $p = 0.04$) with lesser nephrotoxicity (8.4% vs 18.2%) and similar mortality in a prospective double blind RCT.[98] In a recent meta-analysis, 7 RCTs ($n = 1289$) and 8 retrospective cohort/case control studies ($n = 6125$) of MRSA *pneumoniae* patients, linezolid was better than vancomycin in terms of microbiologic cure rates (RR = 0.81, 95% CI, 0.71-0.92), microbiological eradication (RR 0.71, 95% CI, 0.62-0.81) and clinical cure (0.35, 95% CI, 0.18-0.69), without any significant difference in adverse drug effects or mortality.[99] Newer agents have been approved for treatment of CAP. These include omadacycline, delafloxacin and Lefamulin. Omadacycline, a tetracycline derivative, has activity against common CAP pathogens, MRSA, gram-negative bacilli, anaerobes but not against *pseudomonas*, and has been approved in hospitalized CAP patients is US Food and Drug Administration (FDA) approved for the treatment of hospitalized CAP.[100,101] Lefamulin, a pleuromutilin, another antibiotic approved for CAP, is effective against *H. influenzae*, *M. catarrhalis*, *S. Pneumoniae*, MRSA, anaerobes and atypical CAP pathogens, but not against GNBs and *Pseudomonas*.[102,103] Delafloxacin, a quinolone, has activity against gram-positive and gram-negative bacteria, anaerobes, *Neisseria gonorrhoeae*, and atypical respiratory pathogens (*Legionella*, *Chlamydia*, *Mycoplasma*), MRSA and *Pseudomonas* and is efficacious for treatment of lower respiratory tract infections.[104,105]

Evidence Statement

Viruses (including influenza), *streptococcus pneumoniaee*, gram-negative bacilli (including *klebsiella*), *Haemophilus influenzae* and atypical organisms (*Mycoplasma pneumoniaee*) and are common causes of community-acquired *pneumoniae* (CAP) in intensive care unit (ICU). *Staphylococcus aureus*, *Legionella* and *Mycobacterium tuberculosis* are less common causes of CAP in ICU. *Pseudomonas aeruginosa* is an important pathogen causing CAP in patients with structural lung disease. Methicillin resistant *Staphylococcus aureus* (MRSA) and multidrug-resistant gram-negative organisms are relatively infrequent causes of CAP in India and are associated with risk factors such as structural lung disease and previous antimicrobial intake. Anaerobic organisms may cause CAP or co-infection in patients with risk factors for aspiration like elderly, altered sensorium, dysphagia, head and neck malignancy. *S. pneumoniae* remains sensitive to beta-lactams and macrolides. *Haemophilus influenzae* has good sensitivity to beta-lactam with beta-lactamase inhibitors and fluoroquinolones. Recent studies show increasing prevalence of extended spectrum β-lactamase (ESBL) producing *enterobacter*iaceae. Newer agents like omadacycline, delafloxacin and Lefamulin have added advantages of being effective against MRSA and anaerobes. Omadacycline and delafloxacin are effective against GNBs, whereas only Delafloxacin has good sensitivity against *pseudomonas*. Nafcillin and oxacillin are preferred agents for MSSA whereas agents effective against MRSA *pneumoniae* include linezolid, vancomycin and teicoplanin.

What are the Risk Factors for Multidrug-resistant (MDR) Pathogens for CAP in ICU?

Age more than 65 years, chronic respiratory disease, prior antibiotic treatment, prior isolation of resistant organisms from respiratory secretions and presentation with acute renal failure were associated with increased risk of CAP due to multidrug-resistant (MDR) pathogens in prospective observational studies.[106–112] Other factors associated with increased risk of MDR CAP include prior hospitalization for more than 48 hours in the last 3 months, home infusion therapy and patients on renal replacement therapy. Immunosuppression was also considered to be a risk factor for CAP due to MDR organisms.[56]

Evidence Statement

Risk factors for multidrug-resistant (MDR) organisms include age >65 years, antimicrobial therapy in the preceding 3 months, high frequency of antibiotic resistance in the community, hospitalization for ≥48 h in the preceding 3 months, home infusion therapy including antibiotics, home wound care, chronic dialysis within 1 month, family member with MDR pathogen and ongoing immunosuppressive treatment.

Recommendation

- All patients admitted with CAP in ICU should be evaluated for risk factors for infection with MDR organisms (2A).
- Antibiotic therapy should be individualized to cover the commonly implicated organisms according to risk factors, including *Pseudomonas*, ESBL producing *enterobacter*iaceae or MRSA (3A).
- If antipseudomonal, MRSA specific or non-standard antibiotics are initiated emperically, early microbiologic diagnosis of respiratory secretions (Gram stain, PCR or multiplex PCR) and blood cultures should be sought for early de-escalation or narrowing down antimicrobial therapy (3A).

Should Serum Procalcitonin Levels be Done at Baseline in Patients Admitted with CAP in ICU?

Procalcitonin is a promising biomarker for antibiotic stewardship in lower respiratory tract infections (LRIs).[113] Various trials evaluating use of procalcitonin in LRIs tested serum procalcitonin at baseline.[114,115] Serum procalcitonin had an area under ROC curve 0.73 (95% CI, 0.69–0.77) in differentiating bacterial from viral etiology of CAP in a recent meta-analysis.[116] Serum PCT had low sensitivity [0.55 (95% CI, 0.37–0.71) and specificity (0.76, 95% CI, 0.62–0.86) in differentiating bacterial from viral etiology in CAP.[117] Though serum procalcitonin based strategies led to reduction in antibiotic exposure in a meta-analysis of 26 RCTs including 6706 patients, most benefit was attributed to early cessation, and not initiation.[118] In the ProACT trial ($n = 1656$), PCT-based strategy did not show any significant difference in antibiotic expsoure for LRI patients (−0.05 day; 95% CI, −0.6–0.5; $p = 0.87$).[114]

Evidence Statement

Serum procalcitonin has moderate sensitivity and specificity in differentiating bacterial and viral etiology in CAP. Serial measurements of procalcitonin are useful in limiting antibiotic

exposure in ICU patients with lower respiratory tract infections, predominantly by early cessation.

Recommendation

- Serum Procalcitonin should not be used to differentiate bacterial and viral etiology in CAP in ICU (1A).
- Serum procalcitonin levels should be measured at baseline and serially for use in antibiotic de-escalation for CAP in ICU (1A).

How Early should the Antibiotics be Initiated in Patients with CAP Who Require ICU Admission?

In retrospective studies on CAP, initiation of antibiotics within 4 hours of presentation has been associated with reduction in all-cause mortality, regardless of severity [relative risk (RR) 0.24; 95% confidence interval (CI) 0.08–0.71].[119] Systematic review of prospective studies also favored early administration of antibiotics, however, confidence interval was wide (RR 0.82; 95% CI, 0.54–1.24).[119] Recent meta-analysis of retrospective studies also showed decreased all-cause mortality with early administration of antibiotics before 4 hours of hospital admission, especially in severe CAP with *pneumoniae* severity index (PSI) IV to V (adjusted odds ratio, AOR 0.87; 95% CI, 78–97). However, no significant benefit was shown in clinical stability at 48 hours (AOR 1.04; 95% CI, 0.75–1.44), length of hospital stay (AOR 0.92; 95% CI, 84–1.01%) or readmission after discharge (AOR 0.99; 95% CI, 0.88–1.11%).[58] However, all the included studies were retrospective or chart reviews, with low quality of evidence. There was no significant mortality benefit with administration of antibiotics before one hour of recognition of severe sepsis or septic shock (pooled odds ratio 1.46, 95% CI, 0.89–2.4) in a recent meta-analysis. Out of 18 eligible studies, 7 studies were excluded due to non-availability of data confounding the findings.[120] In a recent retrospective study of 35,000 randomly selected inpatients with sepsis, each hour delay in administration of antibiotics was associated with increased odds of in-hospital mortality in patients with sepsis (Odds ratio, OR 1.09; 95% CI, 1.00–1.19; $p = 0.046$), severe sepsis (OR 1.07; 95% CI, 1.01–1.24; $p = 0.014$) and septic shock (OR 1.14; 95% CI, 1.06–1.23; $p = 0.001$).[121]

Evidence Statement

Early initiation of antibiotics has been associated with reduction in all-cause mortality in community-acquired *pneumoniae*, including severe *pneumoniae* with sepsis or septic shock.

Recommendation

- Appropriate antimicrobial therapy should be initiated as early as possible in patients of CAP requiring ICU admission, preferably within the first hour after obtaining necessary microbiologic samples (3A).
- Respiratory samples should be sent for Gram stain, bacterial culture, and other investigations as clinically indicated, as early as possible (3A).
- Multiplex PCR may be used to obtain precise microbiologic diagnosis in patients with CAP admitted to ICU if feasible (2B).

Should CAP in ICU Receive Empirical Antimicrobials or Upfront Targeted Antimicrobial Therapy?

Targeted antibiotic therapy based on *Legionella* and pneumococcal urinary antigen testing was associated with higher relapse rate without any significant differences in clinical failure, length of hospital stay or clinical failure in a randomized controlled trial in patients with severe CAP. However, the study was inadequately powered for outcomes as less than 50% patients had PSI IV and V CAP and only one patient required ICU admission.[122] In another randomized controlled trial, targeted antibiotic therapy based on respiratory secretions cultures, blood cultures, paired serum samples (for *mycoplasma*, *chlamydia* and *coxiella*) and urinary antigens (for pneumococcus and *Legionella*) was similar to empirical therapy in terms of clinical cure, length of hospital stay and late treatment failure or relapse. Study was inadequately powered for ICU patients, though it demonstrated significantly reduced mortality (45% vs 91%; $p = 0.02$) with targeted therapy as compared to empirical therapy.[123] Similarly, in a large retrospective study, targeted antibiotic therapy has been associated with reduced 30-day mortality (AOR 0.64, 95% CI, 0.56–0.74) in CAP, severe CAP (AOR 0.70; 95% CI, 0.54–0.91)and very severe CAP (AOR 0.51,95% CI, 0.40 to 0.64).[58,124] Other retrospective studies have demonstrated limited utility of diagnostic testing to influence prescription modification, clinical cure or failure though lower mortality is reported with targeted therapy (RR 0.37, 0.24 to 0.57).[58,125] Obtaining blood cultures before initiating therapy was associated with mortality benefit in a large retrospective study in 14069 patients with CAP requiring hospitalization.[126] In a multicentric randomized controlled trial of 208 hospitalized CAP patients at risk of GNB infections and indication for bronchoscopy, multiple PCR based therapy was associated with significantly shorter duration of inappropriate antibiotic treatment (38·6 h; 95% CI, 19·5–57·7; $p < 0·0001$) than conventional culture.[127] In another RCT of 294 CAP inpatients, multiplex PCR based point of care (POC) strategy did not show any difference prescriptions of no or narrow-spectrum antibiotics at 4 hours after admission (OR 1.13; 95% CI, 0.96–1.34). However, POC strategy resulted in significant increase in targeted prescriptions at 4 hours (OR 5.68; 95% CI, 2.49–12.94; $p < 0.001$) and 48 hours (OR 4.20; 95% CI, 1.87–9.40; $p < 0.001$). Also, POC strategy was associated with more adequate prescriptions at 48-h (OR 2.11; 95% CI, 1.23–3.61; $p = 0.006$) and on day 5 (OR 1.40; (95% CI, [1.18, 1.66] $p < 0.001$).[128] Multiplex PCR testing of respiratory specimens in 259 hospitalized *pneumoniae* patients showed 96.2% positive agreement and 98.1% negative agreement with routine bacterial culture, and a potential of modification of antibiotic therapy in 70.7% patients, including de-escalation or discontinuation in 48.2% patients.[129]

Evidence Statement

Early institution of targeted antibiotic therapy in severe CAP based on urinary antigen testing is associated with higher relapse rate without any mortality benefit in prospective randomized studies. Retrospective studies have shown mortality benefit with narrowing down of antibiotic therapy based on results from cultures of respiratory specimens, blood cultures as well as *Legionella* and pneumococcal urinary antigen testing. Multiplex PCR based diagnostic testing of respiratory specimens leads to more appropriate and focused antimicrobial therapy administration.

Recommendations

- Empirical therapy covering common etiologic organisms should be initiated for severe CAP requiring ICU admission (2A).
- Investigations including culture of respiratory secretions (sputum, endotracheal aspirate), blood cultures, urinary antigen testing for pneumococcus and *Legionella* may be performed to narrow down therapy. (UPP)
- Multiplex polymerase chain reaction (PCR) testing of respiratory specimens, if available, should be performed for CAP in ICU for

microbiologic diagnosis and subsequent antibiotic modification or de-escalation (3A).
- PCR testing for viral etiology (e.g., influenza, SARS-Cov2) should be performed based on seasonality and local guidelines (3A).
- Bronchoscopic BAL or protected specimen brush samples may be performed for microbiologic diagnosis on case by case basis (3A).

What is the Current Role of Radiologic Investigations in Guiding Antibiotic Therapy for CAP in ICU?

In a recent meta-analysis of 16 studies including 2040 suspected *pneumoniae* patients, pooled sensitivity of ultrasound (0.96) was higher than chest X-ray (0.65) for the diagnosis of *pneumoniae*. Pooled specificity was 0.85 for USG and 0.81 for CXR. The receiver operative characteristics areas under the curve for USG were 0.98 as compared to 0.77 for CXR.[130] Similar results were reported by an earlier meta-analysis.[131] Amongst 140 suspected CAP patients presenting to emergency department, LUS reduced diagnostic uncertainty in CAP from 73% to 14% and led to antibiotic prescription modifications in 32% cases.[132] Claessen et al. prospectively evaluated the impact of Chest CT in 319 suspected CAP patients presenting to emergency department. Of these, 120 patients had no infiltrates on chest radiograph. CT scan revealed parenchymal infiltrates compatible with CAP in 33% ($n = 40/120$) in this group. CT chest also led to exclusion of CAP diagnosis in 29% ($n = 56/188$) patients with infiltrates on chest radiograph. CT chest led to modification in antimicrobial therapy and site of care in 194 (60.8%) patients. These included antibiotic initiation (n-51), antibiotic cessation ($n = 29$), anticoagulation ($n = 3$) and diuretics ($n = 11$).[133] Low dose Chest CT (LDCT) in emergency department led to change in *pneumoniae* probability levels in 54 patients (27%) in another prospective study of 200 elderly patients with suspected CAP.[134]

Evidence Statement

Lung ultrasound has high sensitivity and specificity in diagnosis of *pneumoniae*, and better diagnostic accuracy as compared to chest X ray. Addition of lung ultrasound aids in improving confidence in diagnosis of CAP and leads to significant treatment modification. CT Chest leads to early diagnosis of CAP in ICU and modification of treatment in significant proportion of cases, though there is insufficient evidence in impact on short term outcomes.

Recommendations

- Bedside chest ultrasound should be done for all suspected CAP patients in ICU at baseline, and at frequent intervals as indicated (1A).
- CT Chest may be done for diagnosis of CAP in ICU in cases where diagnosis is in doubt, alternate causes (heart failure, pulmonary embolism) are suspected, to rule out rarer causes (e.g., tuberculosis, *nocardia*) or to decide on site of invasive sampling (bronchoscopy or image guided sampling) (3A).

For Empirical Therapy in Patients with CAP in ICU, should Combination Therapy be Preferred over Monotherapy?

In a recent meta-analysis of CAP patients including 28 observational studies, combination antimicrobial regimens including macrolides have been associated with significantly decreased mortality as compared to non-macrolides (RR 0.82; 95% CI, 0.70–0.97; $p = 0.02$), along with a trend towards mortality benefit favoring macrolides as compared to fluoroquinolones (RR 0.83; 95% CI, 0.67–1.03; $p = 0.09$).[135] Combination therapy also resulted in better survival in patients with shock without any significant increase in microbial resistance.[136] In a matched case-control study of prospectively studied cohorts, combination therapy including macrolides was independent predictor of survival (OR, 0.19; 95% CI, 0.07–0.51) in patients with pneumococcal CAP requiring ICU admission.[137]

Evidence Statement

Empirical combination therapy covering common organisms causing community-acquired *pneumoniae* improves survival without any significant increase in microbial resistance.

Recommendation

- Patients with CAP requiring ICU admission should initially receive combination of empirical antimicrobial agents covering common causative organisms (2A).

What should be the Preferred Combination Therapy for CAP in ICU?

In a recent meta-analysis of 8 studies (1 randomized controlled trial and 7 observational studies), 2273 patients in beta-lactam macrolide arm were compared to 1600 patients in beta lactam-fluoroquinolone arm; beta lactam-macrolide combination was associated with a lower overall mortality as compared to that of beta lactam-fluoroquinolone combination (OR, 0.68; 95% CI, 0.49–0.94; $p = 0.02$) along with decreased length of hospital stay (mean difference, −3.05 days; 95% CI, −6.01 to −0.09; $p = 0.04$).[138] In targeted maximum likelihood estimation and survival analysis of 3775 severe CAP patients, macrolide treatment was associated with significant mortality benefit at 6 months (HR 0.69; 95% CI, 0.60–0.78; $p < 0.001$) and 12 months (HR 0.72; 95% CI, 0.64–0.81; $p < 0.001$).[139] Aztreonam and fluoroquinolones are effective alternatives to macrolides, however, with undue risk of masking and delaying diagnosis of tuberculosis.[140] Aztreonam is effective alternative for patients with contraindication to beta lactams.

Evidence Statement

For patients with severe CAP requiring ICU admission without risk factors for pseudomonal infection, a combination of beta-lactams along with macrolides is better as compared to beta-lactam fluoroquinolone combination in terms of mortality benefit and length of hospital stay.

Recommendation

- For patients with CAP requiring ICU admission, a non-pseudomonal beta-lactam (cefotaxime, ceftriaxone, or amoxicillin–clavulanic acid) plus a macrolide (azithromycin or clarithromycin) should be preferred if there are no risk factors for *Pseudomonas aeruginosa* infection (1A).
- For penicillin-allergic patients, a respiratory fluoroquinolone (levofloxacin, moxifloxacin or ciprofloxacin) and aztreonam may be used (3A).
- If macrolides cannot be used, a fluoroquinolone may be used if there is no clinical suspicion of tuberculosis, after sending sputum or endotracheal aspirate for AFB and Genexpert (3A).

When should Anti-pseudomonal Cover be Added for CAP in ICU? If Required, which are the Preferred Antimicrobials for Anti-pseudomonal Cover?

Age greater than 65 to 70 years, male sex, current smokers, chronic respiratory disease including chronic bronchitis, COPD, asthma or bronchiectasis, cerebrovascular disease, dementia, other chronic neurological disorders, cardiovascular diseases, cirrhosis, immunocompromised states, malignancy, current use of corticosteroids, enteral tube feeding, previous hospital admission, prior respiratory isolation of *pseudomonas*, prior antibiotic therapy and severe *pneumoniae* at presentation have been reported as risk factors for CAP due to *Pseudomonas aeruginosa* in various observational studies.[77,110,111,141–145] In a recent multinational point prevalence study, only 2% of hospitalized CAP patients had drug-resistant *pseudomonas*.[108] Prior antibiotic therapy has been associated with increased risk of multidrug-resistant pseudomonal infection.[143] Use of bronchoscopic BAL and multiplex PCR in 208 hospitalized *pneumoniae* patients with risk factors for gram-negative infection led to 45% reduction in duration of inappropriate antibiotic treatment (difference 38.6 hours, 95% CI, 19.5–57.7) in a multicentric randomized controlled trial.[127]

Antipseudomonal antimicrobial agents include aminoglycosides (gentamicin, amikacin, tobramycin, plazomicin), quinolones (ciprofloxacin, levofloxacin), penicillins (carbenicillin, ticarcillin, piperacillin), carbapenems (meropenem, imipenem, doripenem), polymyxins (polymyxin B, colistin), monobactams (aztreonam), cephalosporins (ceftazidime, cefepime) and fosfomycin. Newer antibiotics (Ceftolozane-tazobactam, Ceftazidime-avibactam, Imipenem-cilastatin-relebactam, Cefiderocol) have proven to be efficacious in the treatment of multidrug-resistant *pseudomonas*.[146]

Evidence Statement

For patients with severe CAP requiring ICU admission, risk factors for infection with *Pseudomonas aeruginosa* include chronic pulmonary disease (chronic obstructive pulmonary disease, asthma, bronchiectasis), frequent systemic corticosteroid use, prior antibiotic therapy, old age, immunocompromised states, enteral tube feeding, cerebrovascular or cardiovascular disease. Prior antibiotic therapy is a risk factor for multidrug-resistant pseudomonal infection.

Recommendation

- If *P. aeruginosa* is an etiological consideration, antipneumococcal, antipseudomonal antibiotic (like ceftazidime, cefoperazone, piperacillin–tazobactam, cefoperazone–sulbactam, imipenem, meropenem or cefepime) should be used (2A).
- Combination therapy should be considered with addition of aminoglycosides or antipseudomonal fluoroquinolones (e.g., ciprofloxacin) (3A).
- If empiric antipseudomonal treatment is started, a culture of respiratory specimens (sputum, miniBAL or BAL) should be obtained to confirm pseudomonal infection or subsequent de-escalation (3A).

When should MRSA Cover be Added to Empiric Regimen for CAP in ICU?

Evidence on CAP due to MRSA is limited, and mostly based on small prospective studies, case series or case reports.[63–66] A systematic review (81 studies; 7 case series, 71 case reports, 3 observational studies) estimated incidence of MRSA CAP to be 0.51 to 0.64 cases per 100,000 population.[63] MRSA CAP carries a high mortality (up to 60%). Close contact with a MRSA carrier or patient, preceding influenza infection, prisoners, professional athletes, army recruits, men having sex with men (MSM), intravenous drug abusers, regular sauna users, immunocompromised status (HIV, acute leukemia, ongoing systemic corticosteroid therapy) and those using antibacterial agents before infection have an increased risk of MRSA CAP.[63,147] Multilobar consolidation, necrotizing consolidation and empyema were also observed in greater proportion of patients with MRSA CAP.[65] Considering multiple risk factors, relatively low frequency but high morbidity and mortality associated with MRSA CAP, the expert group decided to emphasize on thorough assessment of risk factors for MRSA CAP in ICU, while balancing the recommendation to guard against blanket MRSA cover for all CAP cases getting admitted to ICU. The most effective antibiotics against MRSA are vancomycin and teicoplanin. Tigecycline is also effective against MRSA; linezolid has also been reported to be effective in MRSA and VRSA *pneumoniae*.[58,148]

Evidence Statement

Risk factors for MRSA in CAP in ICU include close contact with MRSA carrier or patient, influenza, prisoners, professional athletes, army recruits, men having sex with men (MSM), intravenous (IV) drug abusers, regular sauna users and those with recent antibiotic use. MRSA *pneumoniae* should be suspected after influenza or in previously healthy young patients, if there is cavitation or necrotizing *pneumoniae*, along with rapid increase of pleural effusion, massive hemoptysis, neutropenia or erythematous rashes. Vancomycin, teicoplanin, linezolid and tigecycline are effective antibiotics against MRSA.

Recommendation

- All patients admitted with CAP in ICU should be evaluated for the presence of risk factors associated with MRSA (3A).
- If MRSA is a consideration, empiric linezolid (1A), vancomycin (1A) or teicoplanin (2A) should be added to the regimen. Linezolid should be used for vancomycin intolerant patients, vancomycin-resistant *Staphylococcus aureus* (VRSA), or patients with renal failure (1A).
- PCR and Gram stain of nasal swab, along with Gram stain and culture of respiratory specimens should be obtained for microbiologic diagnosis of MRSA if empiric MRSA treatment is initiated, for future de-escalation or targeted antimicrobial therapy (3A).

When should Anaerobic Cover be Added to Empiric Antibiotic Regimen for CAP in ICU?

Anaerobic organisms were reported to cause the majority of pulmonary infections associated with lung abscesses (26–100%), aspiration *pneumoniae* (62–100%) and empyema (9–76%) in observational studies.[149–157] In a recent observational study of 64 patients with CAP, 15.6% of BAL samples had evidence of anaerobic infection on 16s RNA analysis.[158] Witnessed aspiration, loss of consciousness due to drug or alcohol overdose, seizures with concomitant gingival disease and dysphagia have been considered as risk factors for anaerobic infection.[159] In secondary analysis of a multicentric prospective study of 2606 CAP patients, anaerobic flora was similar in patients with aspiration *pneumoniae* as compared to overall CAP patients. Severe aspiration related CAP patients had higher prevalence of GNBs ($p = 0.02$) and lower prevalence of GPBs ($p < 0.001$). Also, more than 50% of patients received empiric

anaerobic coverage irrespective of presence of risk factors or aspiration *pneumoniae*.[160]

Evidence Statement

Risk factors for aspiration *pneumoniae* in patients admitted with CAP in ICU include dysphagia, altered sensorium, coma, witnessed aspiration, putrid discharge, presence of lung abscess, empyema, or necrotizing *pneumoniae*. There is no significant difference in anaerobic flora of CAP patients with or without aspiration. Severe aspiration related CAP has increased prevalence of GNBs and decreased prevalence of GPCs.

Recommendation

- Empirical antibiotics with anaerobic coverage should be considered for treatment of CAP in ICU in presence of witnessed aspiration, lung abscess, empyema, or necrotizing *pneumoniae* (2A).
- Specific antibiotics with anaerobic coverage (such as clindamycin and metronidazole) should not be routinely prescribed in severe CAP (UPP).

Which Antibiotic should be Preferred for Anaerobic Coverage for CAP in ICU?

Clindamycin was associated with significantly higher cure rates as compared to penicillin in randomized controlled trials in anaerobic lung infections.[154,161] In a randomized prospective study of 100 patients with anaerobic lung infections, ampicillin-sulbactam, clindamycin and panipenem-betamiprom had similar clinical efficacy ($p = 0.62$) and similar duration of treatment ($p = 0.35$) whereas non-clindamycin group had higher frequency of appearance of MRSA (22.7% vs 0%; $p < 0.01$).[162] Ampicillin-sulbactam had similar clinical and bacteriologic response to clindamycin with or without cephalosporin in another prospective randomized multicenter study of 70 patients with anaerobic lung infections.[163] Moxifloxacin demonstrated similar clinical response to ampicillin-sulbactam in a prospective open label randomized multicentric study involving 139 patients with aspiration *pneumoniae* and lung abscess, along with the added advantage of once daily dosing.[164] Moxifloxacin was also shown to be superior to levofloxacin-metronidazole combination in terms of clinical cure at 7 weeks (76.7% vs 51.7%; $p < 0.05$) as well as similar bacteriologic cure (93.3% vs 96.4%, $p > 0.05$) without any significant difference in adverse drug reactions.[165] Duration of treatment has been reported to be variable. Longer duration of treatment (3 to 6 weeks) is required in lung abscesses and empyema.[154,163,164]

Evidence Statement

Commonly prescribed empirical antibiotics for CAP in ICU such as ampicillin-sulbactam, amoxicillin-clavulanic acid, piperacillin-tazobactam and carbapenems have excellent anaerobic coverage. Clindamycin and moxifloxacin are effective against aspiration *pneumoniae* and lung abscess caused by anaerobic organisms. Lung abscess and necrotizing *pneumoniae* may require prolonged treatment up to 4 to 6 weeks.

Recommendation

- Patients with CAP due to anaerobic infection should be initiated on antibiotics with anaerobic activity such as amoxicillin-clavulanate, clindamycin or moxifloxacin (1A).
- Piperacillin-tazobactam or carbapenems can be used for empirical therapy in CAP due to anaerobes if otherwise indicated (3A).
- Duration of treatment should be individualized according to response and severity of disease (3A).

What should be the Optimal Duration of Antibiotics for CAP in ICU?

On post-hoc analysis of a RCT comparing levofloxacin treatment for 5 days to 10 days, subgroup with moderate to high severity CAP had similar clinical cure rates (RR 1.07; 95% CI, 0.95 to 1.2).[58,166] In another study on severe CAP, treatment for more than 7 days did not confer any mortality benefit.[167] However, this study excluded ICU admission, complicated *pneumoniae*, non-responding *pneumoniae* or identification of organisms requiring prolonged treatment. Also, *enterobacter*iaceae, *pseudomonas*, *Legionella* and *S. aureus* was associated with requirement of prolonged treatment.

Evidence Statement

For CAP in ICU, there is limited evidence regarding duration of treatment, with no significant mortality benefit beyond 7 days of antimicrobial therapy in uncomplicated cases. However, CAP due to GNB, *enterobacter*iaceae, *P. aeruginosa*, *S. aureus* bacteremia and *L. pneumophila* requires prolonged treatment. Necrotizing *pneumoniae*, lung abscess, empyema or extrapulmonary infective complications like meningitis or infective endocarditis also require longer duration of treatment.

Recommendation

- Patients with CAP requiring ICU admission should receive antibiotics for 7 to 10 days (2A).
- Patients with CAP due to *Pseudomonas* or aspiration *pneumoniae* should be treated for 14 days (3A).
- Necrotizing *pneumoniae* due to GNB, MRSA or anaerobes also require treatment for 14 to 21 days (3A).
- Duration of treatment should be individualized according to causative organism, response, severity of disease and complications (3A).

What is the Role of Adjunctive Therapy, i.e., Systemic Corticosteroids and Inhaled Antibiotics for CAP in ICU?

Systemic corticosteroid administration for CAP has long been debated. Wan et al. performed a meta-analysis of nine RCTs ($n = 1667$) and six cohort studies ($n = 4095$) evaluating systemic steroids in CAP, and did not find any significant mortality benefit (RR, 0.72; 95% CI, 0.43–1.21) overall or in patients with severe CAP (RCTs: RR, 0.72; 95% CI, 0.43–1.21; cohort studies: RR, 1.00; 95% CI, 0.86–1.17). However, systemic steroids did reduce risk of ARDS (RR, 0.21; 95% CI, 0.08–0.59) and were not associated with significant adverse effects.[168] Prolonged course (20 days) of tapering doses of methylprednisolone did not show any benefit in 60 day mortality (16% vs 18%; OR 0.90, 95% CI, 0.57–1.40) in a multicenter RCT. However, the study was well short of desired sample size, and could recruit only 584 patients against the planned sample size of 1420 patients.[169] A recent meta-analysis of 16 studies involving 3,842 patients with hospitalized CAP patients demonstrated that systemic corticosteroids were associated with reduced need for mechanical ventilation (RR 0.51; 95% CI, 0.33–0.77; $P = 0.001$) and ICU admission (RR, 0.66 [95% CI, 0.45–0.97). However, there was no difference in all-cause mortality (RR, 0.85, 95% CI, 0.67–1.07), treatment failure (RR, 0.78; 95% CI, 0.37–1.67) or incidence of adverse events (RR 1.10; 95% CI, 0.97–1.25). Also, corticosteroid

group had higher hospital readmission rates (RR 1.20; 95% CI, 1.05–1.38).Majority of trials gave corticosteroids for 7–10 days; hydrocortisone 200mg to 240 mg daily dose was the most commonly used regimen.[170] In a subsequent multicenter RCT investigating role of hydrocortisone in severe CAP, 795 patients were analyzed. Hydrocortisone was given as an intravenous infusion of 200 mg over 24 hours for 4 days and continued till 8 or 14 days; intervention arm received hydrocortisone for a median of 5 (IQR3-8) days. Hydrocortisone infusion reduced 28 day mortality (5.6%; 95% CI, –9.6 to –1.7%), reduced incidence of endotracheal intubation (HR 0.59, 95% CI, 0.40–0.86) and need for inotrope initiation (HR 0.59; 95% CI, 0.43–0.82), without any significant increase in adverse events. However, the trial excluded patients with septic shock, pregnancy, immunodeficiency, viral infections (influenza, herpes, acute viral hepatitis), tuberculosis and invasive fungal infection.[171]

Inhaled antimicrobials have been studied as adjunctive therapy in ventilator and hospital-acquired *pneumoniae* and evidence has been summarized in subsequent section.

Evidence Statement

Short course of systemic corticosteroids has been associated with reduced risk of mortality, need for endotracheal intubation and inotrope initiation in severe CAP. Systemic corticosteroids are associated with reduced need for ICU admission and endotracheal intubation in patients hospitalized with CAP, albeit with higher risk of readmission rates. However, large trials have excluded patients with septic shock, pregnancy, immunodeficiency, viral infections (influenza, herpes, acute viral hepatitis), tuberculosis and invasive fungal infections. Hydrocortisone 200 mg to 240 mg daily infusion was most commonly used regimen in CAP trials for 7 to 10 days.

The evidence for inhaled antibiotics is predominantly from hospital-acquired and ventilator-associated *pneumoniae*, with better odds of clinical cure and microbiologic eradication in adjunct inhaled antibiotic therapy.

Recommendation

- Short courses of systemic steroids should be given for patients with severe CAP after careful risk-benefit analysis (1A).
- Hydrocortisone 200 mg infusion over 24 hours for 5 to 7 days should be used for systemic corticosteroid administration in severe CAP patients (2A).
- Inhaled antibiotics may be used in severe CAP patients on a case-to-case basis. (UPP)

Should Procalcitonin be Used to Determine Duration of Antibiotic Administration for CAP in ICU?

In a recent Cochrane meta-analysis of 26 trials involving 6708 patients, procalcitonin utilization for antibiotic discontinuation was associated with reduced mortality (adjusted OR 0.83, 95% CI, 0.70 to 0.99, $p = 0.037$).[118] In an observational cohort study of 352 hospitalized CAP patients, PCT-based therapy led to a 15% cost benefit ($p = 0.005$) and reduced duration of antibiotic therapy (8.6 days vs 12.6 days; $p < 0.001$) without affecting clinical cure rates and mortality.[172] In a randomized multicenter trial of 285 severe CAP patients procalcitonin guidance did not lead to a reduction in antibiotic duration compared to guideline-based clinical assessment (9 days vs 10 days; $p > 0.05$).[173]

Evidence Statement

Serial procalcitonin levels can be used to de-escalate antibiotics for CAP in the ICU without increasing mortality or recurrence rates.

Recommendation

- Procalcitonin levels can be used along with clinical judgement for de-escalation of antibiotics in CAP in ICU in patients treated beyond 5-7 days (1A).

Hospital-acquired *Pneumoniae* and Ventilator-associated *Pneumoniae*

Pneumoniae is one of the commonest hospital-acquired infection. Hospital-acquired or nosocomial *pneumoniae* (HAP) is defined as *pneumoniae* that occurs 48 hours (or more) after admission and did not appear to be incubating at the time of admission. Ventilator-associated *pneumoniae* (VAP) is HAP that develops more than 48 to 72 hours after endotracheal intubation. The previously used term health care associated *pneumoniae* (HCAP) is currently not in use.[174] To provide a more uniform and consistent reporting of cases of ventilator-associated complications, Centers for Disease Control (CDC) has proposed the term ventilator-associated events which includes ventilator-associated condition, infection-related ventilator-associated complication, probable VAP and possible VAP.[175] The incidence of VAP varies among different ICUs and depends upon the definition used. In most ICUs, the incidence is around 10–20%.[174] Endotracheal intubation compromises the natural barrier between oropharynx and trachea as well as facilitates entry of bacteria into lungs.[176] Supine position also facilitates transfer of contaminated secretions leading to VAP.[177] VAP is suspected in patients with new or progressive pulmonary infiltrates plus supportive clinical findings suggestive of infection. The diagnosis is made on clinicoradiologic findings and is supported by isolation of microorganism from lower respiratory tract sample. VAP is associated with overall attributable mortality of 13%, and higher risk of ICU mortality (RR 2.20, 95% CI, 1.91–2.54).[178] VAP leads to significantly longer ICU length of stay and also incur additional hospital costs.[179]

What are the Common Organisms Causing HAP/VAP in ICU and What is their Antibiotic Susceptibility Pattern?

The microorganisms implicated in causation of VAP varies among ICUs. Studies conducted in Western countries demonstrated that majority of VAP episodes are caused by *Staphylococcus aureus* followed by *Pseudomonas aeruginosa*.[180] In a retrospective review of 8474 cases of VAP reported to CDC, *staphylococcus* accounted for 24.1% of cases followed by *pseudomonas* (16.6%) and *klebsiella* (10.1%).[181]

Studies from Asia show preponderance of gram-negative organisms as etiologic agent of VAP. A prospective surveillance study from 73 hospitals in 10 Asian countries from 2008 to 2009 including 2554 cases with HAP or VAP found that *pseudomonas* (15.6%) was most common causative organism followed by *Staphylococcus aureus* (15.5%), *Acinetobacter* spp. (13.6%) and *klebsiella pneumoniaee* (12%). Imipenem resistance of *Acinetobacter* and *P. aeruginosa* was 67.3% and 27.2% respectively. A large proportion of *Acinetobacter* (82%) and *P. aeruginosa* (42.8%) were multidrug-resistant (MDR) while 51.1% and 4.9% were extensively drug resistant (XDR), respectively. The prevalence of MRSA among *S. aureus* isolates was 82.1%.[182] Similarly, another retrospective study from Thailand also found A. baumannii (53.4%) as most common isolate followed by *P. aeruginosa* (35.2%) and MRSA (15.1%).[183]

Multiple studies from Indian ICUs have also shown predominance of gram-negative bacilli (*Acinetobacter*, *pseudomonas* and *klebsiella*) in VAP.[184–186] These gram-negative bacilli are often multidrug-resistant. A prospective study from Pondicherry showed an incidence of VAP to be 18% where *pseudomonas* and *Acinetobacter* were common (21.3%) followed by *staphylococcus* (14.9%).[187] Another study from Karnataka found A. baumannii to be the commonest organism in both early and late onset VAP followed by *pseudomonas*. All isolates of *Acinetobacter* were resistant to at least three antibiotics (i.e. MDR) and one isolate of *Acinetobacter* was pan resistant.[188] There has been also a rise in carbapenem resistance of *Acinetobacter*. A study done by Gurjar et al. from SGPGI showed that 75% patients with VAP due to *Acinetobacter* were carbapenem resistant.[189] Recent data from Indian Antimicrobial Resistance Surveillance Network also showed high prevalence of carbapenem resistant *Enterobacter*iaceae (96%), *Acinetobacter* (80%) and *Pseudomonas* (66.7%); colistin was the only drug with high sensitivity patterns (>90%).[190]

To ensure appropriate therapy and de-escalation, microbiologic diagnosis is important in HAP and VAP. A meta-analysis of five RCTs ($n = 1367$ VAP patients) did not show any mortality benefit of using quantitative or qualitative cultures (RR 0.91; 95% CI, 0.75 to 1.11), and invasive microbiologic sampling as compared to noninvasive sampling group (RR 0.93; 95% CI, 0.78 to 1.11). Also, there was no difference in mechanical ventilation duration, antibiotic modifications or length of ICU stay.[191] Bronchoscopy is a safe procedure overall and in patients with HAP, COPD and acute respiratory failure.[192–194] Use of bronchoscopic BAL led to significant reduction in antibiotic usage in intubated COVID19 patients.[195,196] Bronchoscopic BAL has been the reference standard for the diagnosis of VAP in most studies.[197] A meta-analysis included 25 studies ($n = 1,639$) which analyzed various diagnostic methods for VAP with histopathologic diagnosis as the reference standard. In this meta-analysis, endotracheal aspirate had sensitivity of 75.7% (95% CI, 51.5–90.1) and specificity of 67.9% (95% CI, 40.5–86.8); PSB and BAL were less sensitive (PSB 61.4%, 95% CI, 43.7–76.5; BAL 71.1%, 95% CI, 49.9–85.9) and more specific (PSB 76.5%; 95% CI, 64.2–85.6).[198] Nonbronchoscopic BAL had sensitivity of 0.90 (95% CI, 0.78–1.00)) and specificity of 0.83 (95% CI, 0.72–0.94) when compared to bronchoscopic BAL for diagnosis of VAP in recent meta-analysis.[199] In a prospective study of 652 lower respiratory tract samples with suspected nosocomial *pneumoniae*, multiplex PCR led to significantly higher rates pathogen identification (60.4% to 74.2%) as compared to routine microbiology.[200] In a retrospective multicentric study of 159 *pneumoniae* episodes from France, which included 115 episodes of VAP and HAP, application of multiplex PCR would have led to empiric therapy modification in 77% episodes including de-escalation (40%) and escalation (22%). Application of multiplex PCR would have led to increased appropriate antibiotic therapy administration (87% vs 77%). As compared to routine care.[201]

Evidence Statement

Ventilator-associated *pneumoniae* (VAP) and hospital-acquired *pneumoniae* (HAP) are commonly caused by aerobic gram-negative bacilli, such as *Acinetobacter baumannii, klebsiella pneumoniaee, Pseudomonas aeruginosa,* or by gram-positive cocci (*Staphylococcus aureus*). In Indian ICUs, gram-negative organisms are most common etiologic agents (i.e., *Acinetobacter, Klebsiella and Pseudomonas* spp). Most of these pathogens have been found to be multidrug-resistant. Frequency of specific MDR pathogens causing HAP and VAP may vary by hospital, patient population, type of ICU patient, and change over time. Pan resistant organisms are increasingly being reported. Invasive sampling (including bronchoalveolar lavage) leads to better microbiologic diagnosis in HAP and VAP, but has not been associated with improved outcomes.

Should Baseline Serum Procalcitonin be Measured in Patients with Suspected VAP?

VAP has been associated with higher baseline serum procalcitonin (PCT) levels than controls in small observational studies.[202] In a meta-analysis of 7 studies incorporating 373 patients, PCT had a pooled sensitivity of 76% (69–82), specificity of 79% (74–84), and positive and negative likelihood ratios of 4.35 (2.48–7.62), 0.26 (0.15–0.46) for VAP diagnosis.[203] In a prospective multicenter database of 689 patients, serum PCT could not differentiate VAP from ventilator-associated tracheobronchitis.[204] Use of baseline procalcitonin to decide antibiotic initiation has been discouraged by various international guidelines.[113,174,205] Various trials and studies of antibiotic de-escalation have used a cut off of 80% drop from baseline along with clinical judgement, necessitating which a baseline PCT measurement.[115,118,206–208]

Evidence Statement

Baseline serum procalcitonin has moderate sensitivity and specificity for the diagnosis of ventilator and hospital-acquired *pneumoniae*, and cannot reliably differentiate between ventilator-associated tracheobronchitis and ventilator-associated *pneumoniae*. An 80% decline from baseline procalcitonin levels has been used along with absolute value of less than 0.5 mL to make decisions regarding antibiotic de-escalation.

Recommendation

- Serum procalcitonin should not be used for diagnosis of Ventilator-associated or Hospital-acquired *Pneumoniae* or for decision making regarding antibiotic initiation (1A).
- Baseline procalcitonin levels may be measured in VAP, for future use in antibiotic de-escalation (2B).

What are the Risk Factors for MDR Pathogens in VAP in ICU?

Incidence of VAP caused by MDR organisms has increased in last decade and has been associated with increased cost of care, morbidity and mortality. Data from the early 1980s show that about 50% of mechanically ventilated patient develop VAP within first 4 days after intubation and were due to non-MDR pathogens. However, several recent studies show no significant difference between causative organisms in both early and late VAP.[209] Various factors like advanced age (>60 years) and prior use of antibiotics have been consistently associated with increased risk of MDR organisms.[210,211] In a prospective study done by Trouillet et al. in 135 cases of VAP, the three variables identified as risk factors for MDR VAP were duration of mechanical ventilation (7 days or more) and prior use of broad-spectrum antibiotics (third generation cephalosporins, fluoroquinolones, or imipenem).[212] Renal replacement therapy and septic shock at admission were also found to be risk factors for MDR VAP.[213] Higher Acute Physiology And Chronic Health Evaluation II (APACHE II) score on admission, pleural effusion, prior antibiotic treatment, illicit drug use and tobacco are also found to be risk factors for MDR VAP due to MRSA.[214,215] Similarly, vasopressor use, trauma and neurological emergency

were identified as additional risk factors for MDR VAP.[210] Two studies show that systemic corticosteroid therapy has also been implicated as risk factor for MDR VAP. However, both these studies do not mention the dose and duration for which corticosteroid therapy was used.[210,216] In a recent meta-analysis of 10 studies comprising 4285 patients, Acute Physiology and Chronic Health Evaluation II score (APACHE-II, OR 1.01, 95% CI, 0.73–1.29), Simplified Acute Physiology Score II (SAPS-II, OR 2.81, 95% CI, 0.85–4.76), length of stay in hospital prior to VAP onset (OR 2.64, 95% CI, 0.39–4.89), ICU duration of stay (OR 3.95, 95% CI, 0.89–7.02), Charlson comorbidities index (OR 1.00, 95% CI, 0.89–1.11), overall hospital-stay [OR = 20.742, 95% CI, (18.894, 22.591)], quinolone administration (OR 2.02, 95% CI, 1.34–3.04), carbapenem (OR 3.53, 95% CI, (2.48–5.02), combination of >2 antibiotics (OR 3.18, 95% CI, 2.10–4.81) and prior antibiotic use (OR 2.97, 95% CI, 2.00–4.41) were independent risk factors of MDR bacterial VAP, whereas diabetes and duration of mechanical ventilation did not show any positive correlation with MDR VAP.[217] Hospital settings with prevalence of MDR organisms more than 25% has also been identified as a risk factor for MDR VAP.[205] Other approach has been to emperically use antibiotics against MDR GNBs and *pseudomonas* if their prevalence in local ICU or hospital setting is more than 15%, and to use empiric anti-MRSA antibiotics if local prevalence is >10%. If a patient has risk factors for GNBs and MRSA, empiric regimen covering both is initiated. Various guidelines suggest prescription of empiric antimicrobials based on risk factors for MDR organisms and to target threshold of 90% to 95% of prevalent MDR organisms while treating VAP.[174,205] However, these risk factors have been criticized for having very low specificity.[218] Therefore it is pertinent to obtain a early microbiologic diagnosis to narrow down antibiotic therapy in VAP and HAP.

Evidence Statement

The risk factors for VAP due to MDR organisms include age >60 years, duration of mechanical ventilation ≥7 days, prior antibiotic use within 3 months, presence of severe sepsis or septic shock at time of VAP, ARDS preceding VAP, renal replacement therapy prior to VAP, systemic corticosteroid therapy and high prevalence (>25%) of MDR organisms in the hospital setting.

What should be the Initial Combination of Empiric Antibiotic Therapy for VAP in ICU?

Inadequate or inappropriate therapy for VAP has been associated with higher mortality rates.[219] A Cochrane review included four studies that compared monotherapy to combination antibiotic therapies for VAP. This analysis found no significant difference in primary end point of all-cause mortality and clinical cure rate in intention-to- treat population and clinically evaluable population between monotherapy and combination therapy. Similarly, comparison of combination therapy with optional adjunctive antibiotics (amikacin, vancomycin, linezolid, aztreonam, ceftazidime and tobramycin) did not find any difference in all-cause mortality, clinical cure rate in intention-to-treat population and clinical cure rate in clinically evaluable population. No difference in all-cause mortality or clinical cure rate in intention to treat population was found when carbapenems were compared with non-carbapenems; however, carbapenems had higher chance of clinical cure rate in clinically evaluable population. This meta-analysis supports the use of single antibiotic regimen with understanding that resistance patterns may vary depending upon the local factors.[220] A similar meta-analysis by Infectious Disease Society of America (IDSA) also found no difference between combination therapy versus monotherapy, cephalosporins versus non-cephalosporin regimen, antipseudomonal penicillin versus non-antipseudomonal penicillin regimen and carbapenems versus non-carbapenem regimen. For infections with carbapenemase producing MDR or XDR gram-negative bacteria, a meta-analysis of 53 studies, including 10 studies with *pneumoniae*, reported no mortality benefit or improved clinical cure with combination as compared to monotherapy in RCTs, whereas case series did show mortality benefit (RR 0.83, CI 0.73–0.93).[221] ESBL producing *E. coli* or Klebisella related bloodstream infections had significantly lower mortality with meropenem as compared to piperacillin tazobactam in a RCT of 391 patients.[222] Empiric carbapenems were associated with mortality benefit (RR 0.84; 95% CI, 0.74–0.96; $P = 0.01$) in a meta-analysis of 20 trials including 5489 patients. However, there was a trend towards resistance emergence (RR, 1.40; 95% CI, 0.95–2.06; $P = 0.09$). Also, most quantum of benefit was seen in early VAP trials prior to 2010.[223] In a recent meta-analysis including 9 RCTs, carbapenems were associated with better resolution of *pneumoniae* (OR 1.09; 95 % CI, 1.01–1.17) but had no mortality benefit (OR 0.83; 95% CI, 0.67–1.02) as compared to non-carbapenem regimen in VAP.[224] Among aminoglycoside versus non-aminoglycoside regimen, use of aminoglycoside regimen was associated with less chance of clinical response compared to non-aminoglycoside regimen. When comparing quinolones versus non-quinolone regimen, adverse event rates were less with quinolone regimen [Risk Ratio 0.88 (0.78–0.99) with 95% CI,].[174] A meta-analysis by Walkey et al.[225] found that linezolid was not superior to glycopeptide antibiotics for the end points of clinical success, microbiological success and mortality for patients with MRSA nosocomial *pneumoniae*, without any significant difference in adverse events. However, another meta-analysis found more frequent gastrointestinal adverse effects with the use of linezolid.[226] Colistin and polymyxin B usage has increased in recent years for use in VAP in view of increasing prevalence of multidrug-resistant gram-negative infections.[227] A recent meta-analysis showed no significant difference in unadjusted mortality between colistin and polymyxin B (RR 0.71; 95% CI, 0.45–1.13), however, colistin has increased risk of nephrotoxicity (RR 1.55,95% CI, 1.36–1.78).[228] A propensity score based single center cohort study ($n = 102$) evaluated outcomes for VAP due to carbapenem-resistant *Klebsiella pneumoniaee* and *Acinetobacter* baumannii, and did not find any benefit with tigecycline-polymyxin B combination as compared to high dose tigecycline in terms of 14-day mortality (OR, 0.72, 95% CI, 0.27–1.83), clinical cure (OR, 1.09, 95% CI, 0.48–2.54) microbiological cure (OR, 0.96, 95% CI, 0.39–2.53) and nephrotoxicity (OR 0.85, 95% CI, 0.36–1.99).[229] There was no significant difference in 30 day all cause mortality between colistin monotherapy as compared to combination therapy in multidrug infections (OR OR 0.81, 95% CI, 0.65–1.01).[230] In a multicenter cohort study of 445 patients with *pneumoniae* (CAP, $n = 1$; HCAP, $n = 321$), the authors used guideline-recommended risk factor assessment, and treated patients with >2 risk factors with empiric regimen covering MDR organisms, whereas patients with none or one risk factor were treated with antibiotics for CAP. Using this method, 53% patients required broad-spectrum empiric therapy for MDR organisms, and yet 92.9% patients received appropriate therapy for the identified pathogen.[231]

In a prospective study of 95 BAL and non-bronchoscopic BAL samples of HAP and VAP patients, multiplex PCR had a low turn-around time (4.6 hours), high sensitivity (80%, 95% CI, 73–88%), and specificity (99%, 95% CI, 99–100). Sensitivity for

GNBs was better than that for GPBs (90% vs 62%; $p < 0.005$), with detection of extended spectrum beta-lactamases gene (CTX-M) and carbapenemase genes (NDM, oxa-48) in 75% ($n = 9/12$) cases. Multiplex PCR was simulated to have led to earlier identification of appropriate antibiotic ($n = 20$; 21%) and early de-escalation ($n = 37$;39%) in 37 patients (39%) including de-escalation of empiric carbapenem regimen in 10 cases.[232] Multiplex PCR had a high sensitivity (100%) and specificity (87.2%) as compared to quantitative culture in a multicentric study of 842 prospectively collected respiratory specimens.[233] However, with multiplex PCR, risk of overdiagnosis in terms of detecting resistance genes (15% to 45%) has been highlighted.[234] In a multicentric randomized controlled trial of 206 VAP patients without septic shock, Gram stain based empiric antibiotic regimen was noninferior to guideline based therapy in terms of clinical cure (77% vs 72%; risk difference 0.05, 95% CI, -0.07 to 0.17), with reduced empiric anti-pseudomonal agents (70% vs 100%) and anti-MRSA antibiotics (61% vs 100%).[235] However, the participating ICUs had low MDR GNB prevalence (<10%), and MRSA was the most common organism isolated (50%), thus limiting application in ICUs with high prevalence of NF-GNBs.

It is important to choose appropriate empiric antimicrobials for patients at high risk for MDR GNBs or in ICUs with high prevalence of MDR GNBs. However, in view of high prevalence of carbapenem resistant GNBs, it is important to plan empiric therapy to cover for these pathogens. Approaches to identify Options for empiric treatment for carbapenem resistant GNBs include addition of polymyxins to an antipseudomonal beta lactam, or treatment with newer antimicrobials or beta-lactamase combinations like ceftazidime-avibactam, ceftolozane-tazobactam, imipenem-cilastatin-relebactam, and meropenem-vaborbactam. Other options include aztreonam, tigecycline, minocycline and respiratory fluoroquinolones.

Ceftazidime-avibactam is approved for treatment of HAP or VAP and is shown to have better clinical cure rates and survival benefit in VAP due to carbapenem resistant GNB infections. In a muiltinational phase 3 double blind non inferiority trial randomizing 879 VAP patients, ceftazidime-avibactam met the pre-specified criteria for non-inferiority for clinical cure (68% vs 73% (difference -4·2%, 95% CI, -10·8-2·5) as compared to meropenem (standard treatment group) without any significant difference in adverse events. Common isolated organisms in the study included *Klebsiella pneumoniaee* (37%) and *Pseudomonas aeruginosa* (30%); 28% were not susceptible to ceftazidime.[236] Ceftazidime-avibactam salvage therapy was associated significantly lower 30 day mortality (36.5% vs 55.8%, $p = 0,005$) in a retrospective study of 138 bacteremic carbapenemase producing *Klebsiella pneumoniaee* infected patients.[237] In a meta-analysis of prospective studies and case series (29 studies, 1620 patients), efficacy of ceftolozane-tazobactam, ceftazidime-avibactam and meropenem-vaborbactam was studied. *Pneumoniae* was the most common infection (49.8%); common organisms were MDR *Pseudomonas* (MDRPA, 65.3%) and Carbapenem resistant *enterobacter*iaceae (CRE, 24%). Resistance to the studied antibiotics was seen in 8.9%. Pooled success rate for these antibiotics was 73.3% (95% CI, 68.9%–77.5%).[238]

Ceftolozane-tazobactam was evaluated in a randomized controlled double blind non-inferiority trial in 726 patients with nosocomial *pneumoniae*. As compared to meropenem (control arm), treatment arm had similar 28 day mortality (24% vs 25,3%, weighted treatment difference 1.1%, 95% CI, –5.1 –7.4), clinical cure rates (54% vs 53%, weighted treatment difference 1.1%, 95% CI, –6.2–8.3).[239] Ceftolozane-tazobactam had significantly higher clinical success rates than colistin (72.2% vs 30.3%) in a retrospective, observational study of 51 XDR *Pseudomonas* VAP patients, with higher odds for clinical success (OR 4.47, 95% CI, 1.17–17.08), and lesser nephrotoxicity (11.1% vs 48.5%, $p = 0.01$).[240] In a retrospective study of 200 patients with hospital-acquired infections due to MDR *pseudomonas*, efficacy of ceftolozane-tazobactam was compared with polymyxins and aminoglycosides. 52% of the cases had VAP, 7% had bacteremia and 42% had severe sepsis or septic shock. The ceftolozane-tazobactam arm had significantly less combination therapy (72% vs 15%, $p < 0.001$), higher clinical cure rates (adjusted OR 2.63; 95% CI, 1.31–5.30) and less nephrotoxicity (aOR, 0.08; 95% CI, 0.03–0.22).[241] Ceftolozane-tazobactam has been observed to have *in vitro* activity against 36.4% isolates of *Pseudomonas* with ceftazidime resistance.[242]

Imipenem-cilastatin-relebactam restores activity of imipenem against CRE and *Pseudomonas*, and was non-inferior in terms of 28-day all-cause mortality (15.9% vs 21.3%; difference –5.3%, 95% CI, –11.9%–1.2%) and clinical response (61.0% vs 55.8%; difference 5.0%, 95% CI, –3.2%–13.2%) when compared to piperacillin-tazobactam in a randomized controlled trial of 537 bacterial HAP and VAP. Common pathogens in the trial were *Klebsiella pneumoniaee* (25.6%) and *Pseudomonas aeruginosa* (18.9%).[243] Imipenem-cilastatin-relebactam had higher clinical response (71.4 vs 40 %, difference 26.3% 90% CI, 1.3–51.5), lower mortality (9.5% vs 30%; difference –17.3%, 90% CI, –46.4–6.7), and nephrotoxicity (10.3 vs 56.3%; difference –45.9%, 90% CI, –69.1 to 18.4) as compared with imipenem plus colistin in a double blind RCT of 47 patients with imipenem resistant pathogens.[244]

Meropenem-vaborbactam, another carbapenem-beta-lactamase inhibitor, has activity against carbapenemase resistant *enterobacter*iaceae and had better clinical cure and 28 day all cause mortality when compared to best available therapy in a open label randomized controlled trial of 77 confirmed or suspected CRE infections.[245] Meropenem-vaborbactam had similar mortality and adverse effects as compared to ceftazidime-avibactam in a retrospective study of 131 patients with CRE infections.[246] However, this drug is not effective against carbapenem resistant *pseudomonas* or *Acinetobacter*.

Prolonged infusion of anti-pseudomonal beta-lactams showed mortality benefit (30% lower, RR 0.7, 95% CI, 0.56–0.87) in a meta-analysis of 22 RCTs ($n = 1876$) as compared to rapid infusion in patients with sepsis.[7]

Polymyxin B and colistin have similar microbiologic spectrum. They are highly efficacious against MDR *Pseudomonas*, *Acinetobacter* and *enterobacteriaceae* including *Klebsiella pneumoniaee*. However, colistin is a prodrug, and needs conversion to active drug for efficacy.[247] Pharmacokinetics of polymyxin B ensure rapid achievement of therapeutic levels in plasma, whereas even after giving a loading dose, colistin plasma levels rise slowly and variably, and desired plasma levels of 2 mg/L are difficult to achieve.[248] A multicenter prospective trial comparing combination of colistin and levofloxacin to meropenem levofloxacin combination had to be terminated early due to excessive nephrotoxicity (33% vs 18.8%; $p = 0.012$).[249] Polymyxin B has lesser incidence of acute kidney injury than colistin. Also, colistin achieves high concentrations in the urine due to activation into active form in the urinary tract. For this reason, polymyxin B is preferred in most invasive infections including VAP, whereas colistin is preferred in patients with complicated urinary tract infections.[250]

Aztreonam is a monobactam and acts on bacterial cell wall, though the targets are different than beta-lactams. Also, aztreonam is not degraded by class B metallo-beta-lactamases (e.g., NDM). It is active against gram-negative bacteria including *enterobacter*ieaceae and *pseudomonas*. However it lacks activity against gram-positive organisms, anaerobes, and majority of *Acinetobacter* or *Stenotrophomonas maltophilia*.[251]

Fosfomycin is bactericidal against a variety of gram-negative and gram-positive organisms like *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniaee*, *Enterobacter* spp., *Citrobacter* spp., and *Salmonella typhi*.[252] Intravenous fosfomycin use was reported in 209 ICU patients across 20 centers in Europe. Main indications were CNS infections (21.5%), CAP/VAP (15.3%), bone and joint infections (11%) abdominal infections (11%) and bacteremia (10.5%). MDR pathogens were isolated in 24.4% patients. Fosfomycin was nearly always used in combination with other antibiotics. Clinical success was 81.3% overall and 84.8% in cases with MDR pathogens.[253]

Tetracyclines like minocycline, tigecycline and eravacycline have been considered as potential alternatives to beta-lactams and polymyxins in CRE infections. They function independent of carbapenemases making them potentially useful in treating resistant infections. However, they have rapid distribution into tissue following administration, and thus attain low serum and urine concentrations making them ineffective for bloodstream infections and urinary tract infections. Also, due to bacteriostatic nature of tetracyclines, they need to be used as a part of combination regimen. Tetracyclines can be used for carbapenem resistant *enterobacter*iaceae and *Acinetobacter*, whereas *pseudomonas* are intrinsically resistant to tetracyclines.[254] Minocycline, a tetracycline, has been studied for MDR VAP especially in ICUs with high prevalence of CRE *Acinetobacter*. A recent meta-analysis evaluated the efficacy of combination therapy with minocycline as compared to other combination regimens as controls. Out of 10 eligible studies, 9 were retrospective case series and one was a prospective single center study ($n = 268$). Most common comparators were *colistin* or carbapenem*s*. *Pneumoniae* was the most common infection (80.6%) with VAP in 50.4% cases. Intravenous minocycline had good clinical success (72.6%) and microbiologic success rates (72.6%) with 20.9% mortality.[255] Minocycline was effective in treating *pneumoniae* and bloodstream infections due to GNBs in a prospective study ($n = 71$) with clinical and microbiologic response in 80% patients. The most prevalent gram-negative pathogens in the study were Stenotrophomonas (52%), *Acinetobacter* (30%), and *Burkholderia* (10%).[256] Tigecycline monotherapy was associated with higher mortality as empiric therapy in *pneumoniae* in a meta-analysis.[257] Subsequently, a phase II trial of higher doses of tigecycline monotherapy were compared to imipenem-cilastin in HAP, and had similar efficacy outcomes, without any safety issues.[258] High dose tigecycline demonstrated efficacy in a meta-analysis of 10 studies (n-543) in terms of all-cause mortality (OR 0.44, 95% CI, 0.30–0.66), clinical cure rates (OR 3.43, 95% CI, 2.09–5.63), $p < 0.00001$), and microbiological eradication (OR 2.25, 95% CI, 1.44–3.50) with mortality benefit in subgroup with CRE infections. However, most studies were retrospective, with only one observational study, and one phase II RCT. Also, most studies had given high dose tigecycline in combination with standard background therapy (i.e., beta-lactams, carbapenems, colistin or aminoglycosides).[259] In CRE *Acinetobacter pneumoniae*, tigecycline had similar mortality and clinical cure rates as compared to other regimens, but had significantly lesser microbiologic eradication (OR = 0.43, 95% CI, = 0.27–0.66) highlighting potential concerns for resistance induction.[260] Eravacycline and has been studied in intra-abdominal infections.[261] In a retrospective study of 97 patients with *Acinetobacter* VAP, eravacycline arm had higher mortality and lesser clinical cure and microbiologic eradication rates.[262] Omadacycline is another tetracycline with *in vitro* activity against CRE, but has not been recommended due to PK/PD issues and reduced potency.[263,264]

MDR VAP pathogens have increasing prevalence of resistance against antipseudomonal fluoroquinolones (ciprofloxacin and levofloxacin) and aminoglycosides and therefore, the merit of adding these as a part of combination therapy has been questioned.[174]

Adjunct inhaled antibiotics have been studied in VAP and HAP treatment. In a prospective, multicenter, double-blind, randomized, placebo-controlled, phase 3 study of 725 VAP patients with isolation of MDR GNB or presence or two risk factors for MDR GNB, inhaled amikacin did not demonstrate any mortality benefit (75% vs 77%, OR 0.84, 95% CI, 0.55–1.28; $p = 0.43$).[265] In a recent meta-analysis of eleven RCTs ($n = 1210$), adjunctive inhaled antibiotics improved clinical cure rates (RR 1.13, 95% CI, 1.02–1.26) and microbiological eradication (RR 1.45, 95% CI, 1.19–1.76) in VAP patients without any mortality benefit (RR 1.00, 95% CI, 0.82–1.21).[266] There was no increased risk of renal impairment, however, there was increased risk of bronchospasm (RR 2.74, 95% CI, 1.31–5.73) during treatment. In another meta-analysis evaluating efficacy of adjunct nebulized colistin in VAP treatment, 7 observational studies and three RCTs including 850 VAP patients were included. Nebulized colistin had higher microbiologic eradication (OR, 2.21; 95% CI, 1.25–3.92) without any increase in nephrotoxicity (OR, 0.86; 95% CI, 0.60–1.23). However, nebulized colistin did not improve clinical response (OR, 1.39; 95% CI, 0.87–2.20), mortality (OR, 0.74; 95% CI, 0.50–1.12), duration of mechanical ventilation (mean difference –2.5; 95% CI, –5.20–0.19), or length of ICU stay (MD,–1.91; 95% CI, –6.66–2.84) as compared to intravenous therapy group. In terms of adverse effects, nebulized colistin had higher risk of bronchospasm (OR, 5.19; 95% CI, 1.05–25.52).[267] In a retrospective multicentric cohort study evaluating efficacy of adjunct polymyxin B in 132 VAP patients, there was no significant difference in clinical cure rates (43.2% vs 27.3%, $p = 0.06$), bacterial eradication (36.4% vs 23.9%, $p = 0.132$) and mortality (34.1% vs 42.0%, $p = 0.38$).[268]

For MRSA coverage in VAP and HAP, Linezolid, vancomycin and teicoplanin are commonly used drugs. Linezolid showed better clinical success rates, microbiologic eradication and lesser nephrotoxicity than vancomycin in various trials and meta-analyses.[98,99] Other antibiotics with activity against MRSA include daptomycin, ceftaroline, tedizolid, omadacycline, Lefamulin, Delafloxacin, telavancin and ceftobiprole. Off-label Ceftaroline had success rate of 75% in a retrospective study of 40 MRSA HAP and VAP patients.[269] Tedizolid was compared to linezolid in a RCT of 726 patients with HAP or VAP with suspected gram-positive pathogen, and was found to be noninferior in terms of all-cause mortality (28.1% vs 26.4%, difference 1.8%; 95% CI, –8.2–4.7) but had inferior clinical cure rates (56.3% vs 63.9%; difference 7.6%, 97.5% CI, –15.7–0.5).[270] Telavancin was noninferior to vancomycin in terms of cure rates (82.4% vs 80.7%; 95% CI, for difference, –4.3%–7.7%) in RCT of hospitalized patients with gram-positive HAP and VAP.[271] However, telavancin had lower cure rates and lower survival rates in patients with moderate to severe renal impairment (CrCl <50 mL/minute).[272] Ceftobiprole was evaluated in a RCT of 781 patients with

HAP and VAP, and compared to ceftazidime-linezolid combination. Overall cure rates (50% vs 53%) and microbiologic eradication (63% vs 68%; 95% CI, –16.7 to 7.6) were similar. However, VAP patients had significantly lower cure rates (23% vs 37%) and microbiologic eradication (30% vs 50%; 95% CI, –38.8 to –0.4) in ceftobiprole group.[273] Tigecycline has MRSA activity but has been associated with increased mortality when used for MRSA HAP and VAP.[274]

Evidence Statement

Use of combination therapy for VAP has better outcomes in patients who are at risk for MDR pathogens. Commonly used antimicrobial agents include piperacillin-tazobactam, cefepime, levofloxacin, imipenem and meropenem. Among antimicrobial agents, carbapenems have a higher chance of clinical cure than non-carbapenems. Patients with high risk of MDR HAP or VAP, i.e., those admitted in ICUs with high prevalence of MDR organisms, prior isolation of MDR GNBs from respiratory secretions have been treated with combination therapy of carbapenems or beta-lactams with colistin or polymyxin. Monotherapy with newer beta-lactam-beta-lactamase combinations (e.g., ceftazidime-avibactam) or carbapenem-beta-lactamase combination (e.g., Imipenem-cilastatin-relebactam, meropenem-vaborbactam) have better outcomes and less toxicity as compared to other available regimens or polymyxins. Polymyxin B and colistin have been found to be efficacious in treatment of carbapenem resistant *Klebsiella* and *Acinetobacter*, but colistin has a higher incidence of nephrotoxicity. Tigecycline and minocycline are alternative options for CRE infections when *pseudomonas* is not a consideration. Aztreonam as a part of combination therapy is an alternative when newer beta-lactam-beta lactamase combinations are not available, or in presence of metalloproteinases like NDM. For treatment of VAP due to MRSA, glycopeptides and linezolid have similar clinical success, however, linezolid may be associated with higher chance of thrombocytopenia and gastrointestinal adverse events. Adjunct nebulized antibiotics (colistin, aminoglycosides) have been found to increase microbiologic eradication without any mortality benefit in VAP and HAP.

Gram staining of respiratory secretions can lead to lesser prescription of anti-pseudomonal and anti-MRSA antibiotics without compromising clinical cure rates in ICUs with low MDR organism prevalence. Molecular techniques like multiplex PCR have a very less turnaround time and can be used to effectively modify empiric regimen for HAP and VAP.

Recommendation

- Among patients with VAP who are at high risk of MDR pathogens or are in ICU with high prevalence of MRSA (>15%) and resistant gram-negative organisms (>10%), an agent active against MRSA and at least two agents active against gram-negative organisms including *P. aeruginosa* is recommended (3A).
- Among patients with VAP who are not at high risk of MDR pathogens and are in ICU with high prevalence of resistant gram-negative organisms (>15%) but low prevalence of MRSA (<10%), two agents active against gram-negative organism including *P. aeruginosa* is recommended (3A).
- Linezolid, vancomycin or teicoplanin should be used for empiric MRSA coverage in patients at high risk of MRSA (1A).
- In patients with high risk for MDR GNBs and prior isolation of MDR or carbapenem resistant GNBs from respiratory secretions, monotherapy with newer agents (Ceftazidime-avibactam, Ceftolozane-tazobactam, Imipenem-cilastatin-relebactam or Meropenem-vaborbactam) should be preferred to combination therapy (2A).
- Polymyxin B (preferred) or colistin as part of empiric combination regimen can be used in the ICUs with high prevalence of carbapenem-resistant *enterobacter*iaceae (>20%) in patients with risk factors for MDR or XDR gram-negative pathogens (2A).
- In patients with high risk for MDR GNBs or prior isolation of MDR/carbapenem resistant GNBs from respiratory secretions, tetracyclines (tigecycline or minocycline) may be used as part of combination therapy if no alternate drugs can be given, in patients without bacteremia, and *pseudomonas* is not a consideration (3B).
- In patients with high risk for MDR GNBs, aztreonam can be used as part of combination regimen if no alternate drugs are available or pseudomonal coverage is needed (3A).
- In ICU where distribution of pathogen and antibiotic resistance pattern is known, empiric treatment should be designed accordingly, based upon patient risk factors for MDR pathogens (UPP).
- Adjunct nebulized antibiotics (colistin, aminoglycosides) can be used in combination with systemic therapy for empiric treatment of VAP on case-to-case basis or microbiologic sensitivity (3A).
- Invasive sampling (Nonbronchoscopic BAL or bronchoscopic BAL, protected specimen brushing) should be performed in VAP for microbiologic diagnosis and definitive antibiotic therapy (2A).
- Multiplex PCR of respiratory specimens (non-bronchoscopic BAL, or bronchoscopic BAL) should be used for early identification of causative organisms and appropriate modification of antibiotic therapy (2A).
- Gram stain of respiratory specimens can be used for early de-escalation of empiric anti-MRSA therapy (2A).
- In our country or in areas with high endemicity of tuberculosis, use of linezolid may be restricted unless no suitable alternative is available (UPP).
- Fluoroquinolones and aminoglycosides should be cautiously used as monotherapy in VAP in our country as well as in other areas with high endemicity of tuberculosis. (UPP)

When to Give Antipseudomonal Drugs for VAP in ICU?

Antipseudomonal drugs are often started empirically in VAP when the risk factors for *pseudomonas* infection are high. In a prospective surveillance study, it was found that the odds of developing *P. aeruginosa* VAP were 8 times higher in patients with prior *pseudomonas* colonization than uncolonized patients.[275] In a multicenter study, the independent risk factors for the presence of *P. aeruginosa* were duration of hospital stay ≥48 hours before ICU admission, prolonged duration of ICU stay before enrollment >9 days (highest quartile) versus ICU stay ≤4.8 days (lowest quartile).[276] Risk factors of MDR *P. aeruginosa* include COPD, patients on mechanical ventilation >8 days or patients with >3 previous hospitalizations, and previous use of antibiotics.[277,278]

Evidence Statement

Prior use of antibiotics (most consistent association), prolonged duration of mechanical ventilation, and chronic obstructive pulmonary disease (COPD) have been identified as risk factors for MDR *P. aeruginosa* infection.

Recommendation

- Empiric treatment should be given to cover *Pseudomonas* if there are risk factors for MDR *Pseudomonas* infection (2A).

- In ICUs where gram-negative isolate resistance rate is high (>10 % gram-negative isolate resistant to agent being considered for monotherapy or not known), two anti-pseudomonal antibiotics from different class to be given (3A).

What should be the Duration of Antibiotic Treatment for HAP/VAP?

Prompt initiation of appropriate antimicrobial therapy is the main stay of treatment of VAP. Selection of correct antimicrobial agent must be paired with appropriate duration of therapy in order to optimally treat VAP/HAP. Several studies have evaluated the role of short duration antibiotic treatment in VAP/HAP. A study comparing 8 days therapy to 15 days therapy found no difference in mortality, relapses, mechanical ventilator free days, organ failure free days and length of ICU stay while short course regimen was associated with more antibiotic free days. However, gram-negative bacilli (*P. aeruginosa*) with short course regimen were more likely to have a relapse (40.6% vs 25.4%).[279] A randomized comparison of antibiotic discontinuation policy (discontinuation group) with treating physician teams policy (conventional group) found lower antibiotic duration in discontinuation group without any difference in secondary episode of VAP, hospital mortality or ICU length of stay.[280]

A recent meta-analysis by Dimpoulous et al. reviewed 4 RCTs comparing short (7-8 days) with long (10-15 days) regimens and found increased antibiotic free days with short course treatment with mean difference of 3.4 days($p < 0.001$) and no difference in mortality, clinical and microbiological relapses, mechanical ventilation duration, mechanical ventilation free days and length of ICU stay.[281] In another meta-analysis of 5 studies ($n = 1069$), short and long course antibiotic therapy had similar VAP recurrence (OR 1.48, 95% CI, 0.96, 2.28; $p = 0.08$) overall, and in patients with NF-GNB VAP (OR 1.90, 95% CI, 0.93, 3.33; $p = 0.05$), without any difference in duration of mechanical ventilation, length of ICU stay or mortality.[282]

Evidence Statement

Short-course regimens for VAP are associated with significantly more antibiotic-free days without any significant difference in duration of ICU or hospital stay, recurrence of VAP and mortality. Short-course regimens are associated with more recurrences in VAP due to non-fermenting gram-negative bacilli (NF-GNB).

Recommendation

- Short course (7-8 days) of antibiotic therapy should be used, in case of VAP with good clinical response to therapy (1A).
- Longer duration (14 days) of antibiotic therapy should be considered, in case of VAP caused by NF-GNBs or is associated with severe immunodeficiency, structural lung disease (COPD, bronchiectasis, and interstitial lung disease), empyema, lung abscess, necrotizing *pneumoniae* and inappropriate initial antimicrobial therapy (3A).

When should Anaerobic Cover be Added for VAP and Which is the Preferred Antimicrobial Agent?

Studies have reported variable incidence of anaerobic organism isolation in nosocomial *pneumoniae* occurring in mechanically ventilated patients as isolation of anaerobic bacteria requires adequate transport conditions and special growth media. In a retrospective study in 415 patients, factors associated with anaerobic infection were found to be altered level of consciousness and higher simplified acute physiology score (SAPS).[283] Out of 163 isolates from VAP patients, only one was anaerobic (Veillonella) in a study done by PE Marik et al.[284] Robert et al. evaluated the lower respiratory tract colonization by anaerobic bacteria in ICU patients on prolonged mechanical ventilation. Out of 26 patients, 22 were colonized by at least one bacterial strain and 5 patients developed VAP following colonization and two were attributable to anaerobic bacteria.[285]

Evidence Statement

Incidence of anaerobic bacteria as causative agent of VAP is 2 to 7%. Risk factors for VAP due to anaerobes are altered consciousness, aspiration pneumonitis and high simplified acute physiology score (SAPS).

Recommendation

- Empirical antibiotic regimen for VAP should not include coverage for anaerobic organisms routinely (2A).
- In the presence of risk factors for VAP due to anaerobic pathogens, anaerobic antimicrobial coverage should be added in empirical regimen (2B).
- In patients with risk factors for anaerobic organisms, clindamycin or metronidazole should be added to empirical antibiotics regimen for VAP, if it does not include carbapenems (meropenem or imipenem) or piperacillin-tazobactam in the ongoing empirical regimen (UPP).

When to Give Atypical Cover for VAP and Which is the Preferred Agent?

Atypical bacteria have been implicated as etiologic agents for VAP, however, no sufficient literature exists to assess the size of their role as causative agent in VAP. Incidence of atypical bacteria is variable in various studies. A prospective study utilizing polymerase chain reaction (PCR) amplification method found 9 (15%) cases caused by atypical organisms (5 *mycoplasma*, 3 *Legionella* and 1 *chlamydia*).[286] Another study reported 6 cases of VAP due to *Legionella* among 26 patients with definite VAP.[287] *M. pneumoniae* in 3 patients and C. *pneumoniae* in 2 patients were diagnosed among 100 VAP cases in a study by Apfalter et al.[288] The risk factors for *Legionella* infection include use of cytotoxic therapy and corticosteroids.[289] If *L. pneumophila* is suspected organism for VAP, the combination antibiotic regimen should include a macrolide or a fluoroquinolone rather than an aminoglycoside.[290]

Evidence Statement

Incidence of atypical bacteria as causative agents of VAP is low (5 to 7.5%). Risk factors for VAP due to *Legionella* are *Legionella* colonization in hospital water supply, prolonged use of corticosteroids, cytotoxic chemotherapy, elderly, chronic renal failure, previous antibiotic use, granulocytopenia and poor Glasgow coma score.

Recommendation

- Empirical antibiotic regimen for VAP should not include coverage for atypical organisms routinely (2A).
- In the presence of risk factors for VAP due to atypical bacterial pathogens, atypical antimicrobial coverage should be added to empirical regimen (2B).
- The preferred atypical coverage in combination antibiotics regimen is fluoroquinolones (levofloxacin or moxifloxacin) or macrolides (azithromycin or clarithromycin) (UPP).

Can Serum Procalcitonin be Used for De-escalation of Antibiotic Therapy in VAP?

Procalcitonin (PCT) is a polypeptide precursor to hormone calcitonin and is up-regulated from its normal low serum concentration in response to bacterial endotoxin or mediator of bacterial infection.[291] Measurement of serum PCT has been investigated as biomarker for the presence and persistence of infection, in order to guide decisions for initiation, de-escalation and termination of antibiotic treatment. Delayed initiation of antibiotics in patients with sepsis contribute to increase mortality, while inappropriately prolonged use of antibiotics increases the risk of adverse events, including *Clostridium difficile* infection, and the development of antibiotic resistance. Various studies have evaluated the role of serum PCT in de-escalation of antibiotics. In a multicentric non-blinded RCT comparing guideline based antibiotic discontinuation with procalcitonin based antibiotic discontinuation, procalcitonin group had higher antibiotic free days and reduction in overall duration of antibiotic therapy though the ventilator free days alive, ICU free days alive, length of hospital stay and mortality on 28 days were similar.[206] PRORATA trial found that PCT guided strategy to treat suspected bacterial infection in ICU could reduce antibiotic exposure by 2.7 days with no apparent adverse outcome.[292] Two meta-analyses have also demonstrated increased antibiotic free days in PCT based strategies without negatively affecting the outcome.[293,294] International guidelines differ on using procalcitonin for antibiotic de-escalation in VAP. American Thoracic Society guidelines suggest using PCT plus clinical criteria to guide the discontinuation of antibiotic therapy rather than clinical criteria alone.[174] In contrast, European respiratory Society (ERS) guidelines do not recommend the routine measurement of serial serum PCT levels to reduce the duration of antibiotic course in patients with HAP or VAP when the anticipated duration is 7-8 days although panel mention that they believe in measurement of serial serum PCT levels together with clinical assessment in specific clinical circumstances (such as severely immunocompromised patients, drug resistant pathogens-NF-GNB, and initial inappropriate therapy).[205]

Evidence Statement

Use of procalcitonin to guide de-escalation of antibiotic treatment in patients with VAP is effective in reducing antibiotic exposure, without an increase in the risk of mortality or treatment failure.

Recommendation

- Serum procalcitonin may be used to guide the de-escalation of antibiotics in VAP, when the anticipated duration of therapy is >7–8 days (1B).
- Serum procalcitonin levels (together with clinical response) should be used for de-escalation of antibiotic therapy in VAP in specific clinical conditions (severely immunocompromised patients, drug resistant pathogens-NF-GNB, initial inappropriate therapy) (3A).

How to Approach a Patient of Non-responding VAP?

Non-responding VAP or treatment failure in VAP is defined as the lack of improvement in clinical parameters (48–72 hours) with or without persistence of the infecting microorganism from appropriate sample.[295,296] Various clinical parameters such as the white blood cell count, measures of oxygenation and core temperature have been used in studies to define the normal pattern of resolution of HAP. In a prospective cohort study assessing the resolution of VAP, it was found that temperature normalizes within a median of 3 days and ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/ FiO_2 ratio) improves by 2 days.[297] Another study evaluated bacteriological and clinical efficacy of microbiological treatment of VAP among 76 VAP cases and demonstrated that appropriate antimicrobial therapy for VAP results in the control of the initial infection in 88% of the patients, after day 3 of treatment.[298] There are many implicated causes for non-resolution of VAP. These include wrong diagnosis (such as collapse, mass or pleural effusion), inappropriate initial treatment, delayed initiation of treatment, superinfection, concomitant focus of infection or associated complications in the form of lung abscess, empyema or drug fever.[299,300]

Evidence Statement

Re-evaluation at 48 to 72 hours after the initial diagnosis of VAP is the most suitable time. By then the results of the initial microbial investigation are usually available and treatment modification can be done. Evaluation of treatment response for VAP should be on the basis of clinical, laboratory, radiograph and microbiological results. Factors associated with treatment failure in VAP includes host factors (advanced age, immunosuppressed, chronic lung disease, ventilator dependence), bacterial factors (drug resistant pathogens, opportunistic pathogens), therapeutic factors (inappropriate antibiotics, delayed initiation of therapy, insufficient duration of therapy, suboptimal dosing, inadequate local concentration of drugs), complications of initial VAP episode (lung abscess, empyema), other non-pulmonary infections or non-infectious mimics of *pneumoniae*.

Recommendation

- Non-responding VAP should be evaluated for non-infectious mimics of *pneumoniae*, unsuspected or drug-resistant pathogens, extrapulmonary sites of infection, and complications of *pneumoniae* or its therapy and diagnostic testing should be directed to whichever of these causes is likely (2A).
- CT Chest and other indicated imaging modalities should be performed to clarify diagnosis in non-responding VAP and HAP (3A).
- Microbiologic analysis of blood, respiratory specimen (non-bronchoscopic or bronchoscopic BAL) and other samples like pleural fluid should be performed using conventional culture and molecular methods for identification of pathogens in non-responding HAP and VAP (3A).

Catheter-related Bloodstream Infections (CRBSI)

Intravascular catheters are integral in the management of critically ill patients, especially those who require long-term medical care. They are most commonly used to access the vascular system for the delivery of medication, parenteral nutrition, collection of blood samples and hemodynamic monitoring.[301] CRBSI is defined as the presence of bacteremia originating from an intravenous catheter is a common complication leading to morbidity, mortality and adds to the cost of ICU stay. It is also the most common cause of nosocomial bacteremia in ICUs.[302]

Definition and Diagnosis

Catheter-related Bloodstream Infections (CRBSI) is defined as bacteremia or fungemia in a patient who has an intravascular device

and one positive blood culture result obtained from the peripheral vein, clinical manifestations of infection (e.g., fever, chills, and/ or hypotension), and no apparent source for bloodstream infection (other than the catheter). One of the following should be present, i.e., a positive result of semi-quantitative [>15 colony forming units (CFU) per catheter segment] or quantitative (>10^2 CFUs per catheter segment) catheter culture, whereby the same organism is isolated from a catheter segment and a peripheral blood culture; simultaneous quantitative cultures of blood with a ratio 13:1 of CFU per milliliter of blood (catheter vs peripheral blood); differential time to positivity (growth in a culture of blood obtained through a catheter hub is detected by an automated blood culture system at least 2 hours earlier than a culture of simultaneously drawn peripheral blood of equal volume).[303] Catheter tip colonization (CC) is defined as significant growth of a microorganism (>15 colony-forming units) from the catheter tip culture.[303] CRBSI rates are expressed as CRBSI rate per 1000 central line days. However, the suspicion of CRBSI arises in a patient using any intravascular catheter especially central venous catheter (CVC) who develops new onset fever or chills, unexplained hypotension without any other localizing signs of infection.[302]

What is the Incidence of Catheter Colonization and CRBSI?

Based on United States (US) data from national nosocomial infections surveillance (NNIS) from 1990 to 1994, the CRBSI incidence (per 1000 catheter days) was 4.3 for respiratory intensive care units (RICU), 4.6 for medical-surgical ICUs, 7.3 for trauma ICUs and 12.2 for burn units.[304] Data from NNIS from January 1992 through June 2004 showed that the median rate of CRBSI in ICUs of all types ranged from 1.8 to 5.2 per 1000 catheter days,[305] whereas more recent survey in 2010 showed the mean incidence up to 1.76 per 1000 catheter days, suggesting a decreasing trend.[306]

Data from extended prevalence of infection in intensive care study (EPIC 2) showed an overall point prevalence of 4.7 per 1000 catheter days.[307] In the EPIC III study, 1239 (15.2%) patients had CRBSI with a hospital mortality of 38.1%.[308] A prospective observational study by Lorente et al. showed incidence of CC as 6.04 % and of CRBSI to be 2.79 per 1000 catheter days.[309] Other studies have shown global incidence of CC to be 1.4-20 % while that of CRBSI to be 2.4–12.5 per 1000 catheter days. [310–313] Majority of these studies have shown CVCs as the commonest cause for CRBSIs. The data from India suggest higher incidence of CC and CRBSI. In a study by Mittal et al. CC was found in 59 % catheters with CRBSI rate of 9.5 per 1000 days.[301] Others have shown incidence of CC as 18-42 % while of CRBSI is 1-16.1 per 1000 catheter days.[314,315]

Evidence Statement

The global incidence of CC ranges from 1.4 % to 19.4 % whereas CRBSI incidence ranges from 2.4 % to 12.5 %. The incidence of CC is higher in Indian ICUs ranging from 18 % to as high as 59 %, whereas incidence of CRBSI is up to 16.1 per 1000 catheter days.

What are the Risk Factors for CRBSI?

Incidence of CRBSI varies considerably according to various factors such as the type of catheter (single or multi lumen), duration of indwelling catheters, frequency of catheter manipulation, and patient-related factors such as age, underlying disease and severity of illness. In a retrospective study in 73 events of CRBSI, major risk factors found were advanced age, long-term indwelling catheter, parenteral nutrition, diabetes mellitus (DM), and APACHE II score >23, and more than three underlying diseases. Multivariate analysis showed that an APACHE II score >20 and more than three underlying diseases were independent factors associated with CRBSI occurring within 14 days of CVC insertion.[316] Duration of catheter is an important parameter and catheter duration >14 days is an independent risk factor for CRBSI.[310,313,317–320] Risk for CRBSI is higher when the interval time for dressing change is longer than 48 hours irrespective of the dressing material (permeable or semi-permeable).[312] Use of transparent dressings, regular change of dressings, total parenteral nutrition, and use of three way cannulas have not been consistently associated with increased risk for CRBSIs.[312,317] Regarding hemodialysis (HD) catheters, prospective data by Caylan et al. in 248 patients with HD catheters have shown acute renal disease, administration of antibiotics at the time of catheterization, insertion in the femoral vein, emergency situation for catheter insertion, high number of catheter manipulation, and inadequate hand hygiene prior to catheter manipulations as risk factors of CRBSI.[321] Catheter-related candidemia should be suspected in patients with any of the following risk factors: total parenteral nutrition, prolonged use of broad-spectrum antibiotics, hematologic malignancies, and receipt of bone marrow or solid-organ transplant, femoral catheterization, or colonization due to *Candida* species at multiple sites.[303]

Evidence Statement

Longer indwelling catheter duration, immunosuppression, diabetes mellitus, sepsis at the time of insertion, multilumen catheters and APACHE >23 are important risk factors for CRBSI. APACHE at admission, renal failure, central venous catheterization and steroid therapy are important risk factors for fungal CRBSI.

What are the Common Organisms Causing CRBSI and their Antibiotic Susceptibility?

Apart from severity of the patient's clinical disease and risk factors for infection, initial choice of antibiotics will also depend on the likely pathogens and their susceptibility patterns. According to the available literature, certain organisms should always be considered, apart from taking the local epidemiology into account. National Nosocomial Infections Surveillance (NNIS) survey of nosocomial infections from 1990 to 1999 showed coagulase negative *staphylococcus* (CONS), *Staphylococcus aureus* and enterococcus as common organisms while *Candida* albicans accounted for 5% of the CRBSI. A large proportion of CONS isolates were methicillin resistant and the incidence of MRSA and vancomycin-resistant enterococcus (VRE) was 54.5 % and 25.9 % respectively.[304] According to NNIS 2004 data, 87 % of CRBSI were monomicrobial, out of which 65 % were gram-positive organisms, 25 % were gram-negative organisms and 9.5 % were fungi, with CONS, *Staphylococcus* and *Candida* being the common organisms.[322] During this period, there was 12 % increase in VRE and 11 % increase in MRSA. There was a marked increase in ESBL producing *Klebsiella* with 47 % increase in overall incidence. The proportion of CRBSI due to gram-negative organisms like *Pseudomonas*, *Acinetobacter* and *Klebsiella* is also on rising trends according to recent studies. In a recent observational study, CRBSIs due to *Pseudomonas* and *Acinetobacter* were 22.2% and 20% respectively.[310] This rise in gram-negative organisms has been found in various studies from India as well.[315,316,323,324] In a meta-analysis of 11 studies including 1205 patients with bloodstream infections, Ceftazidime-avibactam had significantly lower 30-day mortality than control groups overall (RR = 0.55, 95% CI, 0.45 to 0.68), when compared to colistin (RR = 0.48, 95% CI, 0.33–0.69),

and in subgroup of CRE producing *Klebsiella* (RR = 0.59, 95% CI, 0.46–0.75).[325]

In Indian ICUs the MRSA incidence ranges from 30% to 87% and that of VRE is as high as 25 %.[323,324] Incidence of ESBL producing organisms has also increased with some studies showing all isolates to be ESBL producing.[326] The proportion of CRBSI caused by fungi varies among different studies and usually ranges from 4.4 % to 20 % and mostly were due to *Candida* albicans.[324,327] However, a prospective observational study from 27 Indian ICUs found *Candida* tropicalis (41.6 %) as the most common cause of fungemia followed by *Candida* albicans (20.9%) and *Candida* parapsilosis (10.9 %). Majority of *C. tropicalis* isolates were sensitive to amphotericin B (99.0 %), azoles (90.1 %), fluconazole (97.4 %) and echinocandins (94.2 %).[328]

Evidence Statement

Coagulase-negative staphylococci (CONS), *S. aureus*, enterococcus and *Candida* species are the common organisms accounting for the majority of the CRBSIs. Large proportion of *Staphylococcus aureus* and CONS are methicillin resistant ranging from 11 % to 87 %. There is an increased incidence of CRBSI due to gram-negative organisms (most of which are ESBL producers) and *Candida* especially the non-albicans *Candida*.

What is/are the Empiric Antibiotic(s) of Choice for CRBSI in ICU?

Empiric treatment, when indicated, should provide coverage against the most frequent organisms causing CRBSI i.e. gram-positive as well as gram-negative organisms. Vancomycin, teicoplanin and linezolid are considered the initial drugs of choice for empiric treatment for gram-positive organisms as the incidence of methicillin resistance is high among CONS and *S. aureus*. A recent meta-analysis by J Li et al. included 7 RCTs comparing linezolid with vancomycin in 5376 patients with MRSA.[329] The clinical cure rate of linezolid group was higher than that of vancomycin group after treatment (OR 1.85; 95% CI, 1.33–2.59, $p < 0.001$) and at follow-up (OR 1.49; 95% CI, 1.17–1.91, $p = 0.001$). However, linezolid monotherapy has not been recommended for empirical treatment of patients with suspected CRBSI.[330] Teicoplanin is a safe and effective alternative to vancomycin considering the lesser toxicity and once daily schedule.[331] Quinupristin-dalfopristin and daptomycin might be alternative drugs effective in MRSA bacteremia and enterococci showing comparable results with vancomycin in RCTs.[332,333] Dalbavancin is another drug belonging to same class as vancomycin and when used in weekly doses, has been shown higher success rate than vancomycin for treatment of CRBSI.[334] For treatment of VRE, a significantly lower mortality rate and trend towards better clinico-microbiologic response has been seen using linezolid as compared to quinupristin-dalfopristin.[335] Apart from gram-positive, an antimicrobial agent with activity against aerobic gram-negative bacilli should be added to the empiric coverage of CRBSI. The appropriate options include aminoglycosides, aztreonam, third-generation cephalosporins with antipseudomonal activity, fourth-generation cephalosporins, piperacillin-tazobactam or quinolones.[303] In patients with risk factors for candidemia empiric treatment against *Candida* is sometimes considered. Caspofungin and fluconazole have equal success cure rates in culture positive *Candida* infections with no difference in mortality as compared to amphotericin B.[336,337] However, increasingly fluconazole resistant *Candida* albicans are being reported in bloodstream infections. Also, non-albicans species with fluconazole resistance, like *Candida* auris are also becoming common in nosocomial settings.[338,339] Echinocandins are therefore being preferred for management of patients admitted in ICU with suspected bloodstream infections due to *Candida* or with *Candida* colonization.[340] Biofire Blood culture identification 2 (BCID2) multiplex PCR panel had high diagnostic accuracy (91.7%) for on-panel pathogens, with overall concordance of 98%.[341] In a multicenter evaluation of BCID2 multiplex PCR panel, the assay correctly classified 90% of gram-negative and 89% of gram-positive bacteria and had mean positive percent agreement of 97% (95% CI, 95-99%) with blood culture; agreement was 67% for *Candida* and 100% for the on-panel targets. However, performance in detection of ESBL encoding genes, or other resistance targets was discordant with blood cultures.[342]

Evidence Statement

Vancomycin, teicoplanin, linezolid and daptomycin are effective in treatment of CRBSI due to MRSA and MR-CONS. Fourth-generation cephalosporin, carbapenem or beta-lactam/beta-lactamase combination like piperacillin-tazobactam and aminoglycosides might be used for gram-negative organisms causing CRBSI. Caspofungin and fluconazole have been equally effective as amphotericin-B for treatment of candidemia. However, increasingly fluconazole resistant *Candida* are becoming more common, and echinocandins are preferred as initial therapy in suspected Catheter-related bloodstream infections due to *Candida*.

Recommendation

- Empirical antibiotic regimen for CRBSI should include coverage for both gram-positive and gram-negative organisms (2A).
- Vancomycin or teicoplanin is the recommended first line drug for the empiric treatment of CRBSI for MRSA and MR-CONS while linezolid and daptomycin are good alternative agents (2A).
- Empiric coverage for gram-negative bacilli should include a fourth-generation cephalosporin, a carbapenem, or a β-lactam/β-lactamase inhibitor combination, newer agents (like ceftazidime-avibactam) or without an aminoglycoside (UPP).
- An echinocandin should be used as empirical antifungal agent for treatment of suspected central line-associated candidemia (2A).

What should be the Duration of Antibiotic Treatment for CRBSI?

Optimum duration of antibiotic treatment to the bare minimum required to treat infections is a reasonable approach to reduce the prevalence of resistance to antibiotics. No significant differences in clinical cure, microbiologic cure and survival were detected among bacteremic patients receiving shorter (5 to 7 days) versus longer duration (7 to 21 days) of antibiotic therapy in a meta-analysis.[343,344] There was 5-10% relapse rate after short course therapy for *Staphylococcus aureus* catheter-associated bacteremia suggesting that short course therapy is acceptable for uncomplicated infections. In case of complicated *S. aureus* infections like infective endocarditis, longer duration (4 to 6 weeks) of treatment is required. Studies have shown similar response irrespective of duration of therapy in gram-negative infections as well. A retrospective study comparing short-course (7 days), intermediate-course (8 to 14 days) and long-course (>14 days) treatment for gram-negative bacteremia has shown similar clinical response rates and microbiological cure. Regarding the duration of empirical antifungals for CRBSIs, there has been no

comparative studies but based on the consensus, approximately14 days of empirical antifungals is recommended.

Evidence Statement

Short duration (<14 days) of antibiotics is as effective as longer duration (>14 days) for uncomplicated *Staphylococcus aureus* bacteremia. Complicated bacteremia due to *S. aureus* or those associated with endocarditis should receive longer duration. For gram-negative bacteremia, seven days of antibiotics is sufficient. In responding patient with uncomplicated CONS infection, 5–7 days therapy is considered optimum. Minimum 14 days treatment with antifungals is required for fungal CRBSI.

Recommendation

- Minimum 2 weeks antibiotics should be given for uncomplicated and 4- 6 weeks for complicated *Staphylococcus aureus* CRBSI and infective endocarditis (2A).
- Minimum 7 days of antibiotics should be given for gram-negative CRBSI (2A).
- Five to seven days antibiotics are recommended for CONS bacteremia (3A).
- For suspected fungal CRBSI, antifungal therapy for at least 14 days is recommended (UPP).

Empirical Antibiotics for Urinary and Urogenital Sepsis in ICU

Urogenital infections in patients in the ICU include urinary tract infection (UTI) and prostatitis in males. The clinical spectrum of UTI includes asymptomatic bacteriuria and funguria to pyelonephritis, and urosepsis with or without obstructive uropathy. Urinary tract infections are the fourth most common type of healthcare-associated infection.[345] UTI additionally account for more than 12% of infections reported by acute care hospitals. About 12%-16% of hospitalized adults have indwelling urinary catheter at some time during their hospitalization. Each day the indwelling urinary catheter is in place, there is 3%–7% increased risk of acquiring a catheter-associated urinary tract infection.[346] UTIs in ICU have different microbiology and higher resistance rates than UTI occurring outside ICU. Urinary tract infection is defined as significant bacteriuria in a patient with symptoms or signs attributable to the urinary tract and no alternate source. Significant bacteriuria in a patient without symptoms or signs attributable to the urinary tract is defined as asymptomatic bacteriuria.

Catheter associated urinary tract infection (CA-UTI) is defined as infection occurring in a person whose urinary tract is currently catheterized or has been catheterized within the previous 48 hours with urethral, suprapubic or intermittent catheterization. It is characterized by symptoms and signs suggestive of UTI with no other obvious source, urine sample (from urinary catheter, or midstream urine for catheter duration less than 48 hours) demonstrating more than 1000 CFU per mL. On the other hand, catheter associated asymptomatic bacteriuria refers to patients with urethral, suprapubic or intermittent catheterization with urine culture positivity (>100,000 CFU/mL) without any signs or symptoms attributable to UTI. According to CDC, CA-UTI is defined as a UTI in patients with an indwelling urinary catheter that had been in place for >2 days on the date of event (day of device placement = D1) and was either present for any portion of the calendar day on the date of event or removed the day before the date of event. Patient should have at least one of the following signs or symptoms: fever, supra-pubic tenderness, costovertebral angle pain or tenderness, urinary urgency, urinary frequency and dysuria along with urine culture with no more than two species of organisms identified at least one of which is a bacterium of $\geq 10^5$ CFU /mL.[347]

What is the Incidence of UTI in ICU? What are the Common Organisms and Risk Factors for UTI in ICU?

The incidence of UTI ranges from 5 to 23 per 1000 catheter days as reported from various observational studies from the West.[348–353] In a observational study, Tay MK et al. from Singapore reported the incidence of UTI from mixed ICU to be 13.7% in patients admitted for more than 48 hours, with the incidence of *Candida* being about 34%.[354] The organisms causing UTI were *Klebsiella* (7%), *E. coli* (7%), polymicrobial (37%) and others (7 %). Female gender, prior antibiotic exposure, duration of ICU and urinary catheter were identified as risk factors for UTI. In a prospective observational study from China, Xie DS et al.[355] reported the incidence of UTI to be 25.5 per 1000 catheter days. Fungi (21.3%) were the most common cause of UTI followed by infection with *E. coli* (17.02%) and *pseudomonas* (10.64%). The risk factors for CA-UTI were duration of catheter for >7 days, benign prostatic hypertrophy and >5 days antibiotic duration. *Pseudomonas* showed absolute resistance to ciprofloxacin, amikacin, ceftazidime, and meropenem. A prospective study by Leone et al. reported incidence of UTI to be 9.6%. The common organisms isolated were *E. coli* (39%), *Pseudomonas* (22%) and *Enterobacter* (15%).[356] Duration of catheterization, length of ICU stay, advanced age, female gender and disease severity score were identified as risk factors for CA-UTI. Similar findings were reported by various studies from western world.[357–360] In the ENVIN registry, gram-negative bacteria were responsible for more than half of the cases of UTI (56.7%) with *E. coli* being the commonest organism isolated (26.7%). Fungal infection was second most common (25.4%) with *Candida* albicans as most common fungus isolated.[361] In a prospective study by Agarwal et al.[314] from Northern India, the organisms causing UTI in ICU included *Acinetobacter* (34.8%), *Pseudomonas* (23.8%) and *E. coli* (15.2 %). Length of ICU stay, renal failure and total parenteral nutrition (TPN) were reported as risk factors for UTI. In a prospective observational study by Habibi et al.[362] including patients with greater than 48 hours of ICU stay, most common causes of UTI were *Candida* spp. (90%) followed by *pseudomonas* (14%) and *E. coli* (10 %). Increased ICU stay and catheterization were identified as risk factors for UTI. Das Gupta et al.[363] reported the incidence of UTI in patients admitted in ICU to be 28%. *E. coli* was the most common organism responsible for UTI (30.8%). Longer ICU stay, catheterization and prior antibiotics use were identified as risk factors for UTI. In a retrospective review by Sahu et al.,[364] incidence of UTI reported was 6.9%. Identified risk factors included longer ICU stay and catheterization.

Evidence Statement

Incidence of CA-UTI ranges from 5-30% of all ICU admissions. The most common organism causing UTI in ICU are gram-negative bacteria (*E. coli, Klebsiella*) and fungi (especially *Candida*). Risk factors for UTI in ICU include duration of catheterization, length of ICU stay, prior antibiotic use, higher disease severity score, and female Gender.

What is the Empirical Antimicrobial Agent of Choice for Treating UTI in ICU?

A systemic review and meta-analysis by Vardakas et al.[365] included 21 studies and 1584 patients with ESBL producing *enterobacter*iaceae bacteremia. He compared the mortality

associated with carbapenems and alternative antibiotics (beta-lactams/beta-lactamase inhibitors) for the treatment of patients with ESBL-positive *enterobacter*iaceae bacteremia. No statistically significant differences in mortality was found between carbapenems and beta-lactams/beta-lactamase inhibitors administered as definitive or empirical treatment for UTI.

In an observational study on gram-negative UTI in hospitalized patients, all isolates were susceptible to carbapenems, with 70 to 80% susceptible to fluoroquinolones, aminoglycosides and cefepime. Organisms were resistant to amoxycillin, amoxycillin-clavulanic acid and co-trimoxazole. gram-negative *enterobacter*iaceae was also resistant to the second and third generation cephalosporins.[366] Another prospective study reported increase in frequency of gram-negative *enterobacter*iaceae and *S. aureus* in catheter associated nosocomial UTI over 10 years, with high sensitivities to amikacin, imipenem, and piperacillin-tazobactam (72.0%, 77.5% and 76.1%, respectively). Lower susceptibility to third-generation cephalosporins and ciprofloxacin (55.2% and 45.0% respectively) were reported. Gram-positive organisms showed high susceptibility to teicoplanin and vancomycin (91.1% and 87.9%, respectively) and low susceptibility to ampicillin and ciprofloxacin (24.1% and 25.5%, respectively).[367] Habibi et al.[362] from northern India reported the antibiotics resistance pattern of gram-negative bacteria causing UTI. In this study, the bacteria were resistant to ceftazidime and netilmicin. Cefoperazone–sulbactam resistance was least common among gram-negative organisms. Sahu et al.[364] reported least resistance to tigecycline, colistin and carbapenems among the gram-negative *enterobacter*iaceae. One study reported antibiotic susceptibility pattern in gram-negative *enterobacter*iaceae and most of the isolates were susceptible to carbapenems, amikacin and levofloxacin.[368] In a RCT, three antibiotics piperacillin-tazobactam, cefepime and ertapenem were compared in terms of clinical and microbiological cure rate and 28 days mortality for treatment of ESBL producing *E. coli*. Both cure rates were high for piperacillin-tazobactam and ertapenem. Cefepime was found least effective in terms of both cure rate and prevention of mortality.[369] In a prospective study, 89.2% of urinary culture isolates were sensitive to fosfomycin; 89.2% of gram-negative bacilli including *enterobacter*iaceae were also susceptible.[370] Patel et al.[371] evaluated *in vitro* activity of fosfomycin against urinary tract *enterobacter*iaceae; 79.16% of the isolates were susceptible to fosfomycin with 92% susceptibility in ESBL producing *enterobacter*iaceae and 72.34% in carbapenem resistant *enterobacter*iaceae (CRE). MDR *enterobacter*iaceae with diverse resistance mechanisms, including ESBL and CRE were found to be susceptible to fosfomycin.

Newer antimicrobial agents and combinations have been studied in MDR UTI infections. In a double blind RCT of complicated UTI patients with clinically suspected GNB infection, ceftriaxone-sulbactam-EDTA was non-inferior to meropenem for co-primary end points of symptomatic resolution (95.9% vs 89.9%, treatment difference 6%, 95% CI, –2.6% to 16%), symptomatic as well as microbiological eradication (94.6% vs 87%; treatment difference, 7.6%; 95% CI, –2.0% to 18.4%), and microbiologic eradication (94.6% vs 88.4%; treatment difference, 6.2%; 95% CI, –3.2% to 16.6%). *Escherichia coli* (n = 113, 80.7%) was the most common organism. ESBL producing pathogens were identified in 119 (83.2%) patients, whereas MDR pathogens were identified in 100 (69.9%) patients.[372] However, ceftriaxone-sulbactam-EDTA did not meet pre-specified efficacy outcome in a RCT of 66 patients with complicated UTI due to Metallo-Beta Lactamase (MBL) producing *enterobacter*iaceae.[373]

Efficacy of Ceftolozane-tazobactam was evaluated in complicated UTI (cUTI) and complicated intra-abdominal infections (cIAI) due to ESBL producing *enterobacter*iaceae in a recent RCT. Most isolates were sensitive to ceftolozane-tazobactam (81.8%) and meropenem (98.3%) whereas sensitivity was low for levofloxacin (25.3%). Ceftolozane-tazobactam had higher cure rates (97.4%) as compared to meropenem (88.5%) or levofloxacin (82.6%).[374] In a multicenter, open label phase 3 trial involving 333 patients with cUTI and cIAI due to ceftazidime resistant *enterobacter*iaceae or *pseudomonas*, ceftazidime-avibactam was noninferior to best available therapy in terms of clinical cure (91%; 95% CI, 85.6–94.7) with comparable adverse effects (31% vs 39%).[375] Meropenem-vaborbactam was compared to piperacillin tazobactam in a phase 3 multinational RCT in 550 patients with cUTI, and was noninferior in terms of overall success (98.4% vs 94%; difference 4.5%, 95% CI, 0.7% –9.1%) and microbial eradication (66.7% vs 57.7%; difference 9.0%; 95% CI, –0.9%–18.7%).[376] Plazomicin, an aminoglycoside with bactericidal activity against MDR *Enterobacter*iaceae, was evaluated in an RCT of cUTI 609 patients and was noninferior to meropenem with respect to composite cure at day 5 (88.0% vs 91.4%; difference, –3.4%; 95% CI, –10.0 to 3.1) and at test of cure visit (81.7% vs 70.1%; difference, 11.6%; 95% CI, 2.7–20.3).[377] Fosfomycin was noninferior to piperacillin-tazobactam in a phase 2/3 RCT of 465 patients with cUTI and acute pyelonephritis, with comparable overall success rate (64.7% vs 54.5%; difference 10.2%; 95% CI, –0.4, 20.8).[378]

The choice of empirical antibiotic therapy is guided by estimates of the likelihood of a resistant organism (as estimated on the basis of epidemiologic data and individual patient risk factors for resistance) and by an assessment of whether the patient will have an adverse outcome if the treatment is inadequate (temporarily) because of a resistant organism. Clinical worsening or lack of any improvement after 1 to 2 days of antibiotic therapy mandates repeat urine culture and imaging to identify whether an obstruction or other anatomical complication is the reason for the lack of clinical improvement. Data is lacking on the optimal treatment duration in cases with severe disease, delayed treatment response, mechanical interventions (including those for hydroureter, stones, abscesses, or necrotizing infection), or other antimicrobial agents.[379] In a descriptive study for the management of febrile UTI among the patients of spinal cord injury with neurogenic bladder, the cure rate was similar for single and dual therapy and duration of antibiotics 10 days as compared to more than 10 days.[380] Among fungal UTI, *Candida* albicans was the most common organism. Both albicans and non-albicans *Candida* were susceptible to imidazoles and fluconazole is the drug of choice.[381,382] IDSA recommends that the patients with CA-UTI who have prompt resolution of symptoms should be treated for 7 days. The patients with delayed response to treatment, regardless of whether the patient remains catheterized or not should be treated for 10-14 days. Levofloxacin should be considered in patients with

CA-UTI who are not severely ill. The regimen of antibiotics for 3 days should be considered for women aged 65 years who develop CA-UTI without upper urinary tract symptoms after an indwelling catheter has been removed.[345]

Evidence Statement

There has been a trend towards increasing prevalence of extended spectrum beta-lactamase producing gram-negative bacteria in the urinary cultures of catheter associated UTI. Aminoglycosides, beta-lactams along with a beta-lactamase inhibitor as well as carbapenems and fosfomycin have good efficacy in catheter associated UTI. The susceptibility for fluoroquinolones is decreasing over time among organisms isolated from nosocomial UTI. *Candida* species isolated from the patients with UTI show sensitivity to fluconazole, but increasingly fluconazole resistance is being reported.

Recommendations

- Initial choice of antibiotics should cover for ESBL producing gram-negative organisms and includes aminoglycosides, beta-lactam along with a beta-lactamase inhibitor or carbapenems (2A).
- In initial empirical regimen for UTI, antibiotics against gram-positive organisms is not recommended (3A).
- In appropriate clinical settings antifungals should be considered in the empirical regimen. Fluconazole is preferred, amphotericin deoxycholate is an alternative if fluconazole resistance is suspected (3B).
- Catheter removal, if no longer indicated, or intermittent catheterization should be done in patients with catheter associated urinary tract infection (3A).

Acute Infective Diarrhea, Antibiotic-induced Diarrhea, and *Clostridium difficile*-associated Diarrhea in the ICU

Diarrhea is defined as the passage of more than three liquid stools in a day.[386] Nosocomial diarrhea is defined as one which arises after 3 or more days of admission to the hospital.[383] Up to 30% of patients in hospital develop nosocomial diarrhea and majority of which have non-infectious etiology. Among infectious causes, *Clostridium difficile*-associated diarrhea is the most common.[384] Overall the incidence of diarrhea in intensive care unit varies between 15-40% in different studies where most cases have a non-infectious or multifactorial etiology.[385]

Etiology of Diarrhea in the ICU

Non-infectious etiologies of diarrhea are commoner in ICU, including enteral feeding, stool impaction and drugs (laxative, prokinetics, histamine antagonists, potassium supplements).[386] Other factors such as sepsis, antibiotic therapy, and hypoalbuminemia increase the likelihood of diarrhea.[387] *Clostridium difficile* is the most common infectious agent associated with diarrhea in the ICU.[388] Infectious etiology is suspected if diarrhea is associated with fever, leukocytosis, vomiting, severe abdominal pain, mucus or blood in stool.[389] Clinical presentation may range from mild infection to life threatening illness with pseudo-membrane formation, toxic megacolon, colonic perforation, sepsis or even death.[388] The American College of Gastroenterology (ACG) have proposed a severity scoring system for *Clostridium difficile* infection.[390]

Diagnosis of Acute Infective Diarrhea in the ICU

Clostridium difficile accounts for the majority of infectious diarrhea in the ICU. Most commonly employed screening test is enzyme immunoassay (for Toxin A and B).[391] Gold standard for diagnosis remains cytotoxin neutralization assay (CCNA) and toxigenic culture, with the latter being more sensitive.[391] Other diagnostic tests include stool glutamate dehydrogenase and polymerase chain reaction techniques. As per *clostridium difficile* infection (CDI) severity index, CDI is defined as severe and complicated if it is associated with any of the following, i.e., hypotension, fever (≥38.5 °C), ileus or significant abdominal distension, mental status changes, leukocytosis (≥35,000 cells/mm^3), leukopenia (<2,000 cells/mm^3), lactic acidosis (>2.2 mmol/L) or end organ failure. Severe disease refers to CDI with hypoalbuminemia (<3 g/dL) along with either abdominal tenderness or leukocytosis (WBC ≥15,000 cells/mm^3). Mild to moderate disease refers to CDAD not satisfying above criteria.[390]

What are the Common Organisms Causing Acute Infective Diarrhea in the ICU?

In a large prospective study, it was reported that infectious etiologies accounted for 9.2% cases of acute diarrhea in a mixed general intensive care unit.[392] *Clostridium difficile* was the most common infective cause accounting for 97 out of the 112 patients in the above study.[392] In Indian studies, incidence of CDI was around 16 – 17%.[393,394] Other organisms include *pseudomonas* aeroginosa and *staphylococcus* which have been associated with sporadic outbreaks of diarrhea in the intensive care unit.[395,396] Viruses are another important cause of infective diarrhea in ICU. Norovirus was isolated in 5.7% cases in one study.[392] Outbreaks of viral diarrhea due to norovirus have also been reported in ICU settings.[397]

Evidence Statement

The incidence of diarrhea in the ICU ranges from 12.9 to 38%. Majority of the cases of diarrhea in ICU are non-infectious in etiology. *Clostridium difficile* is responsible for majority of infectious cases of diarrhea in ICU.

What are the Empirical Antibiotics of Choice for Treating Acute Infective Diarrhea in the ICU?

There is a lack of studies that evaluate the use of empirical antibiotics in patients with diarrhea in the ICU setting. In a prospective study evaluating utility of metronidazole in pre-sumptive *clostridium difficile* diarrhea involving 70 patients, 18 (25%) were subsequently proven to have *clostridium difficile*-associated diarrhea (CDAD) whereas 49 (68%) patients had no identifiable cause. Patients who had CDAD had significant improvement in symptoms as compared to those without it.[398] The American College of Gastroenterology guidelines assert that patients with diarrhea in the ICU who have a strong pre-test suspicion of CDI should receive empirical treatment pending the results of laboratory testing, and even in patients with negative testing, as the negative predictive value of existing tests for CDI are insufficiently high to rule out the infection.[390]

Evidence Statement

Empirical use of metronidazole in patients with diarrhea suspected due to *Clostridium difficile* in ICU setting results in significant symptomatic improvement.

Recommendation

- We recommend that empiric metronidazole be used for therapy of patients with acute diarrhea in the ICU with suspected *Clostridium difficile* infection (3A).

What are the Risk Factors for the Development of CDI or CDAD?

Various factors associated with increased risk of CDI include prior antibiotic use, advanced age, prolonged ICU or hospital stay, immunosuppression, proton pump inhibitor use and enteral feeding. In a recent meta-analysis, prior antibiotic use of second-generation cephalosporins (OR 2.23, 95% CI, 1.47–3.37), third-generation cephalosporins (OR 3.20, 95% CI, 1.80–5.71), fourth-generation cephalosporins (OR 2.14, 95% CI, 1.30–3.52), carbapenems (OR 1.84, 95% CI, 1.26–2.68), clindamycin (OR 2.86, 95% CI, 2.04–4.02), co-trimoxazole (OR 1.78, 95% CI, 1.04–3.05), fluoroquinolones (OR 1.66, 95% CI, 1.17–2.35) and penicillin combinations (OR 1.45, 95% CI, 1.05–2.02) increased the risk of CDAD.[399–409]

Advanced age has been shown to be associated with increased incidence of CDI.[394,410–412] Other risk factors for CDI/CDAD include longer ICU stay, enteral feeding, prolonged mechanical ventilation, and immunosuppression.[388–390,393,400,411–416] Proton pump inhibitors (PPI) have been shown to be independent risk factor for CDAD, possibly due to elevated gastric pH accelerating conversion of C. difficile spores to vegetative forms.[394,417–420]

Evidence Statement

Risk factors for development of CDI include prior antibiotic therapy, advanced age, prolonged ICU/hospital stay, immunosuppression, proton pump inhibitors and enteral feeding. Cephalosporins, clindamycin, fluoroquinolones, carbapenems and penicillin derivatives are the commonly implicated antibiotics for CDAD/CDI.

What is the Recommended Treatment for CDI/CDAD: Which Antibiotics and Duration? Should Offending Antibiotics be Stopped? What is the Role of Probiotics in the Treatment of CDAD? How should Recurrent *Clostridium difficile* Infection be Treated?

While certain antibiotics have a propensity to cause CDI, antimicrobial therapy against C. difficile has been found to be successful in treating CDI in a clear majority of cases. In a Cochrane review that included 22 randomized controlled trials with 3,215 participants, four RCTs directly compared vancomycin and metronidazole for symptomatic cure of CDI.[421–425] It was found that vancomycin was modestly superior to metronidazole for the treatment of CDI with a moderate quality of evidence. However, metronidazole has a much lower cost and an acceptable efficacy for this indication. Fidaxomicin (a newer oral antibiotic with minimal absorption) was non-inferior to vancomycin for treatment of CDI in a multicenter randomized trial.[426] It was more effective than vancomycin in achieving clinical cure when patients were receiving concomitant antibiotics for concurrent infections.[427] There are no direct comparisons between fidaxomicin and metronidazole, however, a network meta-analysis including studies that compared fidaxomicin with vancomycin and vancomycin with metronidazole concluded that fidaxomicin was superior to the other two agents for sustained cure of CDI.[428] Clinical cure rate following oral teicoplanin for management of CDI was comparable with oral vancomycin for management of CDI (96.2% vs 100%, $p = 0.56$).[429] Similar cure rates were reported on comparing teicoplanin with both metronidazole and vancomycin for management of CDI.[425] A pertinent question is whether the offending antibiotic should be stopped during treatment of C. difficile infection. A retrospective review of 246 patients found that the use of implicated antibiotics after the completion of CDI treatment was significantly associated with recurrence of CDI compared to no antimicrobial use (odds ratio [OR] 3.02; 95% CI, 1.66–5.52). On the contrary, the use of the implicated antibiotic during the CDI therapy was not associated with recurrent CDI (OR 0.79; 95% CI, 0.40–1.52).[430] This suggests that treatment of the primary infection may continue, if necessary, with appropriate antibiotic under the cover of CDI therapy.

Use of probiotics in addition to antibiotics for treatment of CDI showed that probiotics reduced the rate of recurrence in patients with recurrent CDI but not in patients with an initial episode.[431] In a systematic review use of probiotics in treatment of CDI was not effective.[432] Whilst probiotics are unsuccessful in treatment of CDI, they have been found to be beneficial for preventing CDI in patients receiving antibiotics. In a review of 26 RCTs, probiotics (including Lactobacillus, Saccharomyces, and combinations) significantly reduced the risk of developing CDAD by 60.5% (RR = 0.395; 95% CI, 0.294–0.531; $p < 0.001$).[433]

Recurrent CDI occurs in up to one-third of the patients and is associated with considerable morbidity and costs. A systemic review that included three studies comparing vancomycin with metronidazole, reported that vancomycin and metronidazole are equally effective in treatment of recurrent CDI.[434–437] Addition of saccharomyces boulardii to vancomycin significantly decreased the recurrence rate (16.7% vs 50%, $p = 0.05$).[437] Fidaxomicin was more effective as compared to vancomycin for recurrent CDI (RR 1.86, 95% CI, 1.04 – 3.31, $p = 0.04$).[426,437] Fecal microbiota transplantation has also been compared to drug therapy for treatment of recurrent CDI. It was found that vancomycin therapy with duodenal infusion of donor feces had relapse free cure rate of 93.8% as compared to 30.8% and 23.1% in vancomycin with bowel lavage and vancomycin therapy alone respectively.[438,439]

Evidence Statement

Both metronidazole and oral vancomycin have similar efficacy in clinical and bacteriologic cure of CDI. Use of implicated antibiotic after completing the treatment of CDI is associated with increased risk of recurrence of CDI. There is insufficient evidence to justify the use of probiotics as an adjunct to antibiotics in the treatment of CDAD. In a single RCT, fecal microbiota transplantation was found to be highly efficacious for treatment of recurrent CDI.

Recommendations

- We recommend metronidazole as the first line treatment of mild to moderate CDI/CDAD (1A).
- We recommend oral vancomycin as the first line treatment of microbiologically proven severe CDI/CDAD (1A).
- We recommend oral vancomycin as the treatment of recurrent CDI/CDAD infection (2A).
- We recommend fecal microbiota transplantation as an alternate treatment of recurrent CDI/CDAD infection (2A).
- We recommend that implicated antibiotics should be discontinued as soon as clinically feasible (2A).

- We recommend against the use of probiotics as an adjunct for the treatment of CDI/CDAD (2A).
- We recommend addition of vancomycin to a patient with microbiologically proven CDI/CDAD, if the patient is already on metronidazole or has no clinical response to metronidazole within 3-4 days (UPP).

Abdominal Infections in ICU

Acute Pancreatitis and Infected Pancreatic Necrosis

Acute pancreatitis (AP) is the inflammatory condition of the pancreas characterized clinically by abdominal pain and raised serum levels of pancreatic enzymes.[440] Majority of the cases are caused by cholelithiasis and chronic alcohol consumption.[441,442] Depending on the severity, AP is divided into mild, moderate and severe. Severity of pancreatitis is based upon the presence of organ failure and complications of acute pancreatitis either local or systemic.[443] Local complications include peripancreatic fluid collections and pancreatic or peripancreatic necrosis (sterile or infected) whereas systemic complications include failure of an organ system (respiratory, cardiovascular, or renal) and exacerbation of a pre-existing disorder (e.g., chronic obstructive pulmonary disease, heart failure, or chronic liver disease).[444] Patients with mild AP have no evidence of organ failure, local or systemic complications. Moderately severe AP is defined by presence of transient organ failure lasting less than 48 hours with or without local and systemic complications. Persistent organ failure for more than 48 hours associated with local and systemic complications defines severe AP (SAP).[440,443] About 20% to 30% of patients with AP develop acute necrotizing pancreatitis.[445,446] Pancreatic necrotic tissue may remain sterile (~70%) or may get infected (~30%). The severity of necrotizing pancreatitis is determined on the basis of the extent of parenchymal involvement by necrosis (i.e.,<30%, 30%-50% and >50%).[447] Infected pancreatic necrosis is associated with higher mortality as compared to sterile necrosis.[448,449] Thus, early recognition and institution of appropriate therapy is necessary. Treatment options include administration of antibiotics and surgical intervention if there is no response to antibiotics.[450,451]

What is the Incidence, Risk Factors and Microbiology of Pancreatic Infection Following Acute Pancreatitis?

Incidence and Risk Factors for Infected Pancreatic Necrosis

Incidence of infected pancreatic necrosis (IPN) in patients with acute pancreatitis varies from 12% to 37% depending upon the patients included (AP vs SAP) and diagnostic modality used for IPN.[452–455] Patients with necrotizing pancreatitis are more prone to develop pancreatic infection and organ failure.[448,449] Greater the extent of necrosis more likelihood of IPN. In a retrospective review of 300 patients of AP, pancreatic infection and organ failure were directly related to the extent of pancreatic necrosis.[454] In a prospective single center study that included 204 patients of AP, pancreatic necrosis of more than 50% was significantly associated with the development of pancreatic infection and multiorgan failure.[455] In a prospective observational study from India, similar findings were reported.[452] Patients of AP can develop organ failure either during early phase (<1 week) known as primary organ failure or during later phase of AP (>1 week) known as secondary organ failure.[456,457] In a prospective observational study in 805 patients of acute pancreatitis, presence of primary organ failure was associated with mortality of 15.8% and was a risk factor for development of infected pancreatic necrosis in 76% of patients.[458]

Evidence Statement

Incidence of pancreatic infection following acute pancreatitis ranges from 12-37%. Presence of pancreatic necrosis of >50% is a major risk factor for pancreatic infection following acute pancreatitis. Primary organ failure predicts development of infective pancreatic infection in patients with acute pancreatitis.

Microbiology of Pancreatic Infection Following Acute Pancreatitis

Enteric gram-negative bacteria including *E. coli, Klebsiella*, *Pseudomonas* and *Enterobacter*iaceae are the most common organisms isolated from IPN.[452,459,460] It has been demonstrated that translocation of enteric bacteria (from the gut) is the main source of infection in necrotizing pancreatitis.[461,462] A recent prospective observational study from India evaluated 209 patients with AP; 108 (52%) developed infected pancreatic necrosis (IPN). Polymicrobial infection was seen in 51% patients. Most common GNB isolated was *E. coli* (32%), E. faecium was the most common gram-positive organism (7%), whereas fungi were isolated in 13% cases. Importantly, 42% of isolates were MDR, whereas 25% were XDR.[463] Gram-positive bacteria including *Staphylococcus aureus*, *Streptococcus* Fecalis, Enterococcus as well as anaerobes, and fungi have also been found.[464,465] There are several studies that reported increase in the incidence of IPN caused by gram-positive organisms especially in patients who received prophylactic antibiotics for the prevention of development of IPN.[455,466–468] Gram-negative organisms isolated from IPN show varying susceptibility to beta-lactam /beta- lactamase inhibitors, aminoglycosides, quinolones and carbapenems. Garg et al. reported that majority of the isolates from IPN were sensitive to third generation cephalosporins and quinolones. A more recent study from India observed that amikacin and imipenem were active against majority of the gram-negative organisms isolated from IPN.[452,460] Resistance in gram-negative organisms to aminoglycosides, quinolones, beta-lactam /beta-lactamase inhibitors as well as to carbapenems has increased over last few decades. However, they remain sensitive to colistin and tigecycline. Gram-positive organisms remained sensitive to vancomycin, linezolid and teicoplanin.

Evidence Statement

Gram-negative organisms are the most common organisms isolated from infected pancreatic necrosis following acute pancreatitis in Indian patients. Prophylactic antibiotic use in patients of AP to prevent IPN has been associated with increased risk of infection with gram-positive organisms. Resistance to carbapenems, beta-lactam /beta- lactamase inhibitors and quinolones in gram-negative organisms isolated from IPN has increased, however, with maintain sensitivity to colistin and tigecycline.

What are the Empirical Antibiotics of Choice for Treatment of Pancreatic Infection Following Acute Pancreatitis?

Initial reports on use of prophylactic antibiotics in patients with AP to prevent IPN was associated with reduction in the incidence of IPN and mortality, however, well designed RCTs and meta-analysis

failed to confirm the advantage of prophylactic antibiotics.[469–471] Antibiotics should be prescribed in patients with evidence of IPN (positive image guided FNA or surgical specimen) or suggested by presence of air within the necrotic pancreatic tissue or persistent fever with leukocytosis and multiorgan failure.[450,451] Empirical antibiotic regimen is selected based upon the local susceptibility pattern, pharmacokinetic properties of antibiotics and previous antibiotic exposure. Gram-negative organisms isolated from IPN show varying susceptibility to aminoglycosides, cephalosporins, quinolones, piperacillin-tazobactam and carbapenems. Over the past few decades there is an increase in the resistance among GNBs isolated from IPN to cephalosporins, quinolones, piperacillin-tazobactam and carbapenems with maintained sensitivity to colistin.[472] Various pharmacokinetic studies have demonstrated the existence of blood pancreatic barrier and this barrier is responsible for the selective uptake of antibiotic drugs into the pancreas.[473,474] These studies demonstrate that carbapenems have the highest while as aminoglycosides have least penetration to pancreatic tissue.[474]

Duration of antibiotic therapy in patients with IPN is not clear. However, Malaysian Society of Intensive Care suggests that duration should be guided by serial assessment of clinical and radiological response.[475] There are multiple case series, observational studies and meta-analysis which suggest that conservative management with use of antibiotics in patients with IPN is associated with improved outcome and less mortality as compared to surgical debridement.[476–480] Percutaneous drainage or endoscopic necrosectomy should be considered if the patient fails to improve or deteriorates clinically.[450,451]

Evidence Statement

Prophylactic use of antibiotics in patients with necrotizing pancreatitis has not been shown to reduce incidence of pancreatic infection and mortality. Presence of persistent fever, leukocytosis, multiorgan failure and presence of air within pancreatic necrosis suggest infected pancreatic necrosis. Cephalosporins, piperacillin-tazobactam, quinolones and carbapenems have the highest whereas aminoglycosides have the lowest penetration into necrotic pancreatic tissue. Response to antibiotic therapy is assessed by clinical and radiological parameters.

Recommendation

- Routine use of prophylactic antibiotics to prevent pancreatic infection following acute pancreatitis of any severity is not recommended (1A).
- Empirical antibiotic regimen in patients with infected pancreatic necrosis should be guided by local microbiological data, susceptibility pattern, pharmacokinetic property of antibiotics and previous antibiotic exposure (UPP).
- In treatment-naïve patients with evidence of infected pancreatic necrosis, we recommend empirical treatment with either carbapenems, piperacillin-tazobactam or cefoperazone-sulbactam (2A).
- In patients not responding or already exposed to the piperacillin-tazobactam, cefoperazone- sulbactam or carbapenems, colistin should be added to the empirical regime (3B).
- Duration of antibiotic therapy should be guided by clinical, radiological and laboratory parameters (UPP).
- Patients not responding to antibiotics should undergo necrosectomy and drainage (3B).

Biliary Sepsis

Acute Cholangitis

Acute cholangitis (AC) is a bacterial infection of the biliary tract that commonly occurs in an obstructed system and leads to systemic signs of infection. Choledocholithiasis is the most common cause of acute cholangitis.[481] AC is classified as mild, moderate, and severe based on organ dysfunction and various biochemical abnormalities.[482] Grade III AC is associated with organ dysfunction that includes any of the following: hypotension requiring either inotropic or vasopressors, confusion, PaO_2:FiO_2 ratio <300, serum creatinine levels>2 mg/dL, an international normalized ratio >1.5 or platelet counts $<100 \times 10^9$/L. Grade II cholangitis is associated with any two of the following conditions: WBC count >12,000/mm^3 or <4,000/mm^3, high fever (≥39°C), age >75 years, hyperbilirubinemia (>5mg/dL) or hypoalbuminemia. Grade I do not meet any of the grade III or grade II criteria. Management of acute cholangitis depends on the severity of the illness and include administration of antibiotics and biliary drainage to relieve the obstruction. Drainage can be done electively in patients with mild cholangitis, within 24-48 hours in patients with moderate cholangitis and immediately in case of severe cholangitis.[483]

What are the Incidence, Risk Factors, and Microbiology of Biliary Infection in ICU?

Incidence and Risk Factors

The incidence of acute cholangitis varies with underlying etiology. In patients with cholelithiasis, symptomatic acute cholangitis develops in 0.2%-9% of cases.[484,485] The incidence of acute cholangitis after endoscopic retrograde cholangiopancreatography (ERCP) ranges from 0.4% to 10%.[486,487] Risk factors for acute cholangitis include obstruction of the biliary tree (choledocholithiasis, biliary stricture, cholangiocarcinoma, periampullary carcinoma, stent placement for biliary drainage or worm infestation) or biliary intervention (ERCP, post-surgical biliary stricture).[488–492]

Evidence Statement

Incidence of acute cholangitis varies with underlying etiology and ranges from 0.2 to 10%. Cholelithiasis, choledocholithiasis, benign and malignant common bile duct (CBD) strictures, CBD interventions, and stenting are the most common risk factors for cholangitis.

Microbiology of Acute Cholangitis

Various observational studies among patients with acute cholangitis from India and across the world have reported that gram-negative enteric organisms are the most common pathogens isolated from bile and/or blood.[490,493–498] In patients with nosocomial acute cholangitis e.g., postoperative state, with indwelling biliary stents or those with malignant biliary obstruction, more resistant organisms such as MRSA, VRE, and *pseudomonas* are frequently detected as causative microorganisms. Risk factors for MDR organisms causing acute cholangitis include previous hospitalization and antibiotic use within 90 days.[492] Although the bacteriological profile of acute cholangitis has remained stable over the last few decades, their antibiotic susceptibility pattern has changed. Most of the gram-negative isolates show varying sensitivity to carbapenems, piperacillin-tazobactam, cefoperazone-sulbactam, aminoglycosides, and quinolones, with increased resistance to cephalosporins and penicillins.[490,492,494–497, 499]

Evidence Statement

Gram-negative organisms are the most common organisms isolated from patients with acute cholangitis. Most of the pathogens isolated are susceptible to third-generation cephalosporins (such as cefoperazone-sulbactam), aminoglycosides, quinolones, ureidopenicillins, and carbapenems. Risk factors for multidrug drug resistance organisms causing acute cholangitis include an indwelling biliary stent, malignant biliary obstruction, previous hospitalization, and antibiotic use within 90 days.

What is the Empirical Antibiotic Rgimen for Acute Cholangitis?

Empirical antibiotic regimen in patients with acute cholangitis depends on the antimicrobial activity against causative bacteria, the severity of cholangitis, past history of antimicrobial administration to the patient, local susceptibility patterns (antibiogram) of the suspected causative organisms, and biliary penetration of the antimicrobial agents.[500] Biliary obstruction reduces the antibiotic concentration within the bile and improves after biliary drainage, therefore should be considered in all patients of acute cholangitis.[483] Tokyo guidelines for the management of acute cholangitis suggest monotherapy with beta-lactam/ beta lactamase inhibitor (cefoperazone-sulbactam, piperacillin-tazobactam) or carbapenems or fluoroquinolone plus metronidazole to cover anaerobes.[501] IDSA suggests combination of beta-lactam/ beta-lactamase inhibitor (BL/BLI) or carbapenems or quinolones with metronidazole for moderate to severe community-acquired cholangitis. For nosocomial moderate to severe cholangitis combination of BL/BLIs or carbapenems or quinolones with metronidazole plus vancomycin is advised.[502] IDSA suggests that antimicrobial therapy of established infection should be limited to 4–7 days, unless it is difficult to achieve adequate source control.[502] Previous Tokyo guidelines recommended antibiotics for 2-3 days in case of mild and 5-7 days in case of moderate to severe cholangitis.[501] However, latest revised Tokyo guidelines for management of acute cholangitis suggest duration of antibiotic to be 4-7 days once the source of infection iscontrolled.[500] Duration of antibiotics may be guided by clinical response. Empiric antifungal therapy is usually not warranted.

Evidence Statement

The empirical antibiotic regime in patients with acute cholangitis is guided by the severity of the disease, local antibiotic susceptibility pattern, and biliary penetration of the antibiotics. The duration of antibiotics depends on the severity of cholangitis and adequacy of source control. Biliary drainage (percutaneous or endoscopic) is required in addition to antibiotic use in the management of acute cholangitis.

Recommendation

- Empirical antibiotic therapy should be guided by the severity of the cholangitis, local microbiological susceptibility patterns, biliary penetration of antibiotics, and previous antibiotic exposure (UPP).
- We recommend either beta-lactam/ beta-lactamase inhibitor (such as cefoperazone-sulbactam or piperacillin/tazobactam) or carbapenems (imipenem/meropenem) as monotherapy in patients with moderate to severe cholangitis (3B).
- We recommend antibiotic duration for 4-7 days in patients with acute cholangitis after adequate source control (2B).
- Biliary drainage should be considered in all patients with cholangitis in addition to empirical antibiotic therapy (1A).
- Anti-anaerobic therapy (such as metronidazole, tinidazole, or clindamycin) is required if a biliary-enteric anastomosis is present and the primary antibiotic therapy does not include carbapenems, piperacillin/tazobactam, or cefoperazone/ sulbactam as these drugs have sufficient anti-anaerobic activity (3A).

Liver Abscess

A liver abscess is an infectious, space-occupying lesion in the liver. Pyogenic and amoebic liver abscesses are the two most common causes of liver abscess. Appropriate initiation of antibiotics will help to prevent potentially lethal complications like bacteremia and the spread of abscesses to other organs.

Incidence and Risk Factors

The incidence of pyogenic liver abscess varies from as low as 2.3 per lac population to as high as 446 per lac depending upon the presence of risk factors that predispose the person to liver abscess.[503,504] The various risk factors for pyogenic liver abscess include male gender, older age, diabetes mellitus, biliary diseases, endobiliary procedures, alcoholism, hepatobiliary malignancies, and infected cystic liver lesions.[504–508]

What are the Most Common Organisms Causing Liver Abscess in ICU?

Microorganisms causing liver abscess have shown varying trends over the years. The earlier studies had shown predominantly gram-positive organisms like *streptococcus* as common cause of pyogenic liver abscess.[509] However, recent studies have reported gram-negative organisms (including *Klebsiella pneumoniaee*, *E. coli*, and *P. aeruginosa*) to be responsible for the majority of cases of pyogenic liver abscess.[505,506,510–514] Rarely pyogenic liver abscess is caused by organisms like *Burkholderia*, *Prevotella* and anaerobic bacteria including *Eikenella* and *Peptostreptococcus*.[515–517] In Indian setting, amoebic liver abscess is the most common cause of liver abscess caused by infection with Entamoeba histolytica.[514] The *Streptococcus milleri* group (including *Streptococcus anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*) is also an important cause of liver abscess in western world and usually suggests a disseminated infection.

Evidence Statement

Amoebic liver abscess is the most common cause of liver abscess in Indian setup. The incidence of pyogenic liver abscess varies from 2.3 to 446 per 100,000 hospital admissions per year. Gram-negative organisms (*E. coli* and *Klebsiella*) are the most common organisms causing pyogenic liver abscess. Risk factors for pyogenic liver abscess include diabetes mellitus, older age, male gender, biliary diseases, biliary procedures, alcoholism, malignancy, intra-abdominal infection, and cystic lesions in the liver.

What are the Empirical Antibiotics of Choice for Treating Liver Abscess in ICU?

Amoebic Liver Abscess

Empirical treatment of amoebic liver abscess consists of a combination of a tissue agent and a luminal agent. Metronidazole is the drug of choice for the management of amoebic liver abscess. Metronidazole given for a period of 10 days has been

shown to be effective.[517] Alternatives to metronidazole include tinidazole, ornidazole, and nitazoxanide.[518,519] The luminal agents used to remove any intraluminal cysts include paromomycin, diiodohydroxyquin or diloxanide furoate, even if the stool microscopy is negative. Routine use of drainage of amoebic liver abscess is not indicated in uncomplicated cases.[517] However, the addition of needle aspiration to metronidazole has shown to hasten clinical improvement , especially in a large abscess (5 cm to 10 cm).[514] Surgical intervention is required if there is no response to medical management.[517,520]

Evidence Statement

Metronidazole is the drug of choice for the treatment of amoebic liver abscess. The optimum duration of treatment in patients with amoebic liver abscess is 7-10 days. Routine needle aspiration of amoebic liver abscess is controversial. Addition of aspiration to drug therapy in patients with amoebic liver abscess of >5 cm in size hastens clinical improvement.

Recommendation

- We recommend metronidazole as an initial antibiotic of choice in patients with amoebic liver abscess (2A).
- We recommend antibiotic treatment for a period of 7-10 days in patients with amoebic liver abscess (3B).
- Needle aspiration of amoebic liver abscess is recommended in patients with a lack of clinical improvement in 48-72 hours, left lobe abscess, abscess more than 5-10 cm or thin rim of liver tissue around the abscess (<10 mm) (UPP).
- The luminal agents used to remove any intraluminal cysts (paromomycin, diiodohydroxyquin or diloxanide furoate) should be used even if the stool microscopy is negative (UPP).

Pyogenic Liver Abscess

Antibiotics that are effective in the treatment of pyogenic liver abscess include third and fourth-generation cephalosporins (such as ceftriaxone, and cefepime), aminoglycosides, fluoroquinolones, beta-lactam/beta-lactamase inhibitor (piperacillin-tazobactam), carbapenems, and metronidazole.[511,521–523] Carbapenems are effective for the treatment of liver abscess caused by melioidosis or infection with ESBL producing organism.[524,525]

The empirical regimen should include a broad-spectrum parenteral antibiotic pending microbiologic analysis of the abscess contents. It should cover enteric gram-negative bacilli, *streptococci*, and anaerobes. Antibiotic therapy should generally be continued for four to six weeks.[512] However, the optimal duration of therapy is unclear and is guided by the clinical and radiological response. Studies have reported that shorter courses of antibiotics for 2-4 weeks are effective as well.[512,521,526] In case of abscess cavity with a size less than 5 cm, a needle aspiration is preferred and in case of abscesses more than 5 cm in size, percutaneous catheter drainage is preferred.[527–529] Surgical drainage is required in cases of abscesses with viscous contents obstructing the catheter, an underlying disease requiring primary surgical management and inadequate response to percutaneous drainage within 7 days.[530]

Evidence Statement

Beta-lactam/beta-lactamase inhibitors, metronidazole, and carbapenems are effective antibiotics for management of pyogenic liver abscess. Carbapenems are effective in case of suspected infection with ESBL producing organisms or melioidosis. Antibiotics are required for prolonged periods ranging from 4-6 weeks. Clinical and radiological assessment is required to guide the adequate treatment duration. Initial 2-4 weeks therapy may be parenteral while oral therapy may be given for rest of the duration.

Recommendation

- We recommend beta lactam/beta lactamase inhibitors with metronidazole in patients with pyogenic liver abscess for a duration of 4-6 weeks (2A).
- We recommend carbapenems in case of infection with ESBL-producing organisms or melioidosis (2B).
- The empiric regimen should also cover *E. histolytica* until the causative pathogen is found or amebic abscess is excluded (UPP).

Peritonitis

Peritonitis is defined as an inflammation of the peritoneum from any cause. Peritonitis occurs due to a variety of etiologies, of which the most common is infections. It is broadly classified as primary, secondary, and tertiary. Primary peritonitis, also known as spontaneous bacterial peritonitis (SBP), has no identifiable anatomical dehiscence. It is usually managed non-surgically. The risk factors for the development of primary peritonitis include advanced cirrhosis, nephrotic syndrome, and peritoneal dialysis.[531,532] Secondary peritonitis is the infection of peritoneum that occurs in critical ill patients secondary to organ perforation, anastomotic leak or trauma to the gastrointestinal tract. Tertiary peritonitis may be defined as a severe recurrent or persistent intra-abdominal infection after apparently successful and adequate surgical source control of secondary peritonitis.[533] It leads to prolonged systemic inflammation and is usually associated with high mortality (30-64%). Longer ICU stay, emergency abdominal surgery and total parenteral nutrition are risk factors associated with the development of tertiary peritonitis.[534–539]

What are the Most Common Organisms Causing Peritonitis in ICU?

Enteric gram-negative organisms including *E. coli*, *klebsiella* and *enterobacter*iaceae are the most common causative agents for primary and secondary peritonitis.[540,541] Other organisms include gram-positive bacteria(such as enterococcus)as well as anaerobes (i.e. bacteroides).[541] Tertiary peritonitis is usually due to opportunistic and nosocomial drug resistant bacteria and fungi. Various organisms reported are enterococcus, *Candida*, *staphylococcus* and *enterobacter.*[539,542]

Evidence Statement

The risk factors for development of primary peritonitis are decompensated cirrhosis, nephrotic syndrome and peritoneal dialysis. The risk factors for development of secondary peritonitis include intra-abdominal organ perforation, post intra-abdominal surgery, and trauma. Longer ICU stay, urgent operation on hospital admission, total parenteral nutrition, and stomach-duodenum as primary infection site are associated with the development of tertiary peritonitis. Gram-negative enteric organisms (such as *E. coli*, and *Klebsiella pneumoniae*) are the common causes of primary and secondary peritonitis. Other organisms include gram-positive as well as anaerobic bacteria. The organisms commonly isolated in tertiary peritonitis are *Candida*, Enterococcus faecium and *Staphylococcus* epidermidis.

What are the Empirical Antibiotics of Choice for Treating Peritonitis in ICU?

Primary Peritonitis

Cephalosporins and fluoroquinolones are effective against the majority of the cases of primary peritonitis.[540,543–546] Antibiotics for a period of 5–7 days are effective in SBP.[540,543,547,548] In difficult to treat SBP, cefepime and imipenem are reported to be effective.[549]

Secondary Peritonitis

The antibiotics effective in secondary peritonitis are beta-lactam/beta-lactamase inhibitors (piperacillin-tazobactam), quinolones, carbapenems (Imipenem with Cilastin), aminoglycosides, and metronidazole.[541,550,551] When enterococci are considered, the addition of vancomycin or linezolid is required for a spectrum adequacy rate of more than 95%.[552] Community-acquired infections of mild to moderate severity can be treated with Cefoxitin, Cefotetan, Cefmetazole, Ticarcillin-clavulanic acid.[553]

The average duration of antibiotic therapy is 10 to 14 days. However, recently the emphasis is on a shorter course of antibiotics after adequate source control. The recent STOP –IT trial has found that in patients after an adequate source control, outcomes after fixed-duration antibiotics (approximately 4 days) were similar to those after a longer course of antibiotics (approximately 8 days).[554]

Evidence Statement

Third-generation cephalosporins are the most effective antibiotic therapy for primary peritonitis. Antibiotics are usually required for 7-10 days for adequate treatment. Most of the organisms isolated in secondary peritonitis are sensitive to beta-lactam/beta-lactamase inhibitors or carbapenems. For gram-positive organisms, vancomycin and linezolid are effective treatment options. Short duration of antibiotic treatment (4 days) is as effective as a longer duration after adequate source control.

Recommendation

- We recommend third generation cephalosporins (such as cefotaxime and ceftriaxone) for a duration of 7-10 days in patients with primary peritonitis (2A).
- We recommend either beta-lactam/beta-lactamase inhibitor or carbapenems with an anaerobic cover (using metronidazole) for the treatment of secondary peritonitis (2A).
- For secondary peritonitis, antibiotic treatment is required for at least 4 days after an adequate source control; however, longer treatment is required if adequate source control is not achieved (2A).

CNS Infections in ICU

Infections of the central nervous system (CNS), either community or hospital-acquired, are frequent causes of admission to the ICU. Bacterial meningitis and brain abscesses are one of the most common CNS infections and can result in significant morbidity and mortality. CNS infections are markedly different from systemic infections because of closed anatomic space and immunologic isolation of CNS from the rest of the body. They often have nonspecific clinical manifestations posing a diagnostic challenge to the clinician. Early suspicion, rapid diagnosis, and aggressive management are essential for better outcomes and to prevent various complications and neurological sequelae.

What are the Most Common Organisms Causing Acute Bacterial Meningitis in ICU?

Bacterial meningitis, an infection of the meninges and subarachnoid space, is a complex disorder in which injury is caused partly by the causative organism and partly by the host inflammatory response. Bacterial meningitis is a medical emergency, given the associated mortality and neurological sequelae requiring prompt recognition, rapid diagnostic evaluation, and emergent antimicrobial therapy. Hence accurate information regarding the incidence, risk factors, and microbiological profile of bacterial meningitis is necessary to ensure appropriate empirical antibiotic management. Meningitis can be community-acquired or associated with a variety of neurosurgical procedures (e.g., craniotomy, placement of invasive neuro-monitoring techniques, external ventricular drain catheters, or cerebrospinal fluid shunts) and penetrating head injury. The latter group is classified as nosocomial meningitis or healthcare-associated meningitis and ventriculitis. Both groups differ in their pathogenic mechanisms, risk factors, etiological agents microbial susceptibility patterns and hence are discussed separately.

Community-acquired Meningitis

The incidence of bacterial meningitis in the USA was 2 cases per 100,000 population in 1998–1999 that decreased to 1.38 cases per 100,000 population in 2006–2007; the most common organisms were *Streptococcus pneumoniaee* (56.8%), *Neisseria meningitidis* (17.2%), group B *streptococci* (16.7%), *Haemophilus influenzae* (5.8%) and *Listeria monocytogenes* (3.2%).[555,556] In a retrospective study of 195 culture positive acute bacterial meningitis patients, the most common organism was *streptococcus pneumoniaee* followed by *Staphylococcus aureus* and *klebsiella pneumoniaee*.[557] Various large studies have found *S. pneumoniae* as the most common etiological agent followed by *N. meningitidis*, *L. monocytogenes*, *H. influenzae* and group B *Streptococcus*.[558–562] Though *S. aureus* has also been reported as one of the common etiological agents in some studies.[559–560] Otitis media, immunocompromised status, elderly population, and prior use of antibiotics have been described as risk factors for bacterial meningitis.[558,563,564] Various Indian studies have yielded similar results.[565–568] The prevalence of meningitis in hospitalized and critically ill patients of all age groups (0–75 years) varies from 8.68% and 78.85% in India. *Streptococcus pneumoniaee* is the predominant pathogen causing meningitis across different regions of India, with a frequency ranging from 4% to 61.8%.[569,570]

Evidence Statement

The incidence of community-acquired pyogenic meningitis ranges from 2 to 7.40 per lakh population and data suggest higher incidence in children. The common causative organisms include *streptococcus pneumoniaee*, *Neisseria meningitidis*, other *streptococci*, *Haemophilus influenzae* and *Listeria monocytogenes*. Other causative organisms are *staphylococcus* species, gram-negative bacilli, and *Pseudomonas*. Common risk factors for community-acquired bacterial meningitis are otitis media, elderly population, depressed immune status and prior use of antibiotics.

Nosocomial Meningitis

Nosocomial meningitis may result from various invasive procedures including craniotomy, placement of internal or external ventricular catheters, lumbar puncture, intrathecal infusions of medications, spinal anesthesia or complicated head trauma or rarely from metastatic infection in patients with hospital-acquired bacteremia.

Incidence of post-ventricular drain or catheter-related infections have been studied in many retrospective and prospective studies and ranges from 5.6% to 14.2% and 5.5% to 19% respectively.[571–576] A systematic review from January 1990 through March 2008 reporting on ventriculostomy and extraventricular drain (EVD) related CNS infections described an incidence of 2–27%.[577] *Staphylococcus* epidermidis (70%) is the most common microbiological agent followed by gram-negative bacilli (15%) and *Staphylococcus aureus* (10%). Risk factors described included EVD duration greater than 11 days, frequency of cerebrospinal fluid (CSF) sampling, intraventricular hemorrhage, and surgical technique (subcutaneously tunneled EVD, Rickham reservoir with percutaneous CSF drainage). Post craniotomy or neurosurgery incidence of meningitis ranges from 0.02% to 9.5%.[573,578–584] Most of the studies have reported *staphylococcus* to be the most common causative organism.[573,578,580,582,583] Few studies have also reported *Acinetobacter* and *Enterobacter*iaceae as the most common organisms.[579,581] Postoperative CSF leak has been consistently shown to be a risk factor.[573,578–580,582,583,585] Other risk factors are placement of external shunts, longer duration of drainage, multiple intracranial operations, emergency or prolonged surgery, diabetes, and elderly population.[573,578–583] The role of prophylactic antibiotics for post-neurosurgery and craniotomy meningitis has been debatable, however, a recent meta-analysis of 7 RCTs including 2365 post-craniotomy patients found that prophylactic antibiotic use reduced the rate of post neurosurgical meningitis.[586] The incidence of post-spinal blockade meningitis is very low with a large retrospective analysis of 12,60,000 spinal blockades and 450,000 epidural blockades showing incidence to be 1 in 53,000 with alpha-hemolytic *streptococci* as the most common causative organism.[587] Exogenous inoculation is a risk factor and various measures such as hand disinfection, sterile gloves, face masks and operating caps decrease the risk of development of meningitis.[588] The incidence of meningitis or ventriculitis in patients with post-traumatic head injury is 1.39%-2%.[589,590] Common organisms include CONS, gram-negative bacilli, and *Acinetobacter*. Lumbar and ventricular drains are described as the risk factors. A recent Cochrane systematic review has not shown benefit of using prophylactic antibiotics in patients with basilar skull fracture, independent of CSF leakage.[591] Post-internal ventricular drain infections incidence has been reported between 5.9% to 15.2% in various prospective and retrospective studies. Most common causative organisms included *Staphylococcus aureus* and CONS.[592,593] Postoperative CSF leak, use of single gloves and number of times shunt system exposed to breached surgical gloves were described as risk factors.[594,595] Indian studies suggest a 0.7–8.9% incidence of meningitis in post-neurosurgical patients.[596] There have been reports of such infections with MDR organisms and newer antibiotics such as Ceftazidime-avibactum have been used for the same.[597]

Evidence Statement

Incidence of post-ventricular drain or catheter meningitis ranges from 2% to 27%. Commonly implicated organisms are CONS (especially *staphylococcus* epidermidis), *Staphylococcus aureus*, *Acinetobacter*, *pseudomonas*, and *Enterobacter*iaceae. Risk factors are repeated catheterization, higher catheter duration, CSF sampling, presence of concomitant systemic infection, and surgical technique i.e., subcutaneously tunneled extraventricular drain (EVD), Rickham reservoir with percutaneous CSF drainage. The incidence of post craniotomy or post neurosurgery meningitis is 0.02% to 9.5%. Most commonly implicated organisms are *Staphylococcus aureus*, coagulase-negative staphylococci (especially S. epidermidis), *Enterobacter*iaceae, *Acinetobacter*, and *pseudomonas*. Risk factors include CSF leak, EVD, longer duration of drainage, multiple operations, lack of antibiotic prophylaxis, and emergency surgery. The incidence of post-neuroaxial blockade meningitis is 0.2 per 10000 with *Viridans streptococci* and *Staphylococcus aureus* being common organisms. Exogenous inoculation is the main risk factor. Post-head trauma meningitis incidence ranges from 1.39% to 2% with CONS, *Acinetobacter*, and *Enterobacter*iaceae as common microbes and prolonged hospitalization, and insertion of a lumbar and ventricular drain as common risk factors. Post-internal ventricular drain infection incidence ranges from 5.9% to 15.2%. The most common causative organisms are CONS, *Staphylococcus aureus*, gram-negative bacilli, group D *streptococci*, and *Propionibacterium acnes*. CSF leak, single gloves use, and number of times shunt exposed to breached surgical gloves are the risk factors.

What are the Empirical Antibiotics of Choice for Treating Acute Bacterial Meningitis in ICU? What should be the Duration of Antibiotic Treatment?

Early diagnosis and urgent appropriate antimicrobial therapy along with other adjunctive therapy is necessary to reduce morbidity and mortality associated with bacterial meningitis. As isolation of microorganisms takes time and sometimes it may not be isolated at all, empirical antimicrobial therapy needs to be based on the most likely involved organism as determined by the presence of risk factors for various organisms and local antibiotic susceptibility patterns.

Community-acquired Meningitis

The evidence regarding empirical antibiotic choice in acute bacterial meningitis (ABM) is limited.[598] A retrospective study found reduced penicillin susceptibility in 23% of patients with meningitis, including 16% in community-acquired meningitis. Ceftriaxone combined with penicillin was found adequate in 97% cases.[599] Retrospective study by Hakam Erdem et al. reported the inadequacy of ceftriaxone alone in the treatment of pneumococcal meningitis in view of increasing penicillin resistance in pneumococci worldwide.[600] A Cochrane review in 2007 comparing third-generation cephalosporins (ceftriaxone or cefotaxime) with conventional antibiotics (ampicillin-chloramphenicol combination, or chloramphenicol alone) as empirical therapy for ABM in adults and children found no statistically significant difference between the groups in the risk of death, risk of deafness or risk of treatment failure although significantly decreased chances of culture positivity of CSF after 10 to 48 hours with the third generation cephalosporins at the cost of increased risk of diarrhea.[601] A recent Indian study including 266 culture-positive ABM patients (including 142 CAM patients) found that gram-positive pathogens exhibited maximum sensitivity to vancomycin and linezolid whereas most gram-negative pathogens were sensitive to carbapenems.[602] Seven days antibiotic therapy has been recommended for *N. meningitidis* and *H. influenzae*, 10-14 days for *S. pneumoniae*, 14–21 days for S. agalactiae, 21 days for aerobic GNB and 21days or more for *L. monocytogenes*.[603]

Evidence Statement

Choice of antibiotics depends on the most likely causative microorganisms, local antibiotics sensitivity patterns, mechanism

of infection, and patient's predisposing condition. Most commonly recommended empirical antibiotic regimens include third-generation cephalosporin plus vancomycin, third-generation cephalosporin monotherapy and penicillin monotherapy. Addition of amoxicillin, ampicillin or benzyl-penicillin has been recommended in patients older than 50 years. However, antibiotic therapy should be modified according to the isolated organisms since MDR organisms are being reported from community as well.

Recommendation

- We recommend third-generation cephalosporin (preferably ceftriaxone) plus vancomycin as empirical antibiotics of choice for community-acquired meningitis (3A).
- We recommend adding ampicillin or amoxicillin if the age >50 years (3A).
- If beta-lactams are contraindicated, we recommend chloramphenicol plus vancomycin as the antibiotic of choice, and to add cotrimoxazole if age >50 years (3A).
- We recommend ciprofloxacin or aztreonam plus vancomycin as an alternative regimen and to add cotrimoxazole, if age greater than 50 years (UPP).
- We recommend the duration of antibiotics based on suspected or isolated organisms i.e., 10 to 14 days for *streptococcus pneumoniaee*, 14 to 21 days for *Streptococcus agalactiae*, 7 days for *Neisseria meningitidis* or *Haemophilus influenzae*, 21 days for aerobic gram-negative bacilli, and 21 days or more for *Listeria monocytogenes* (3A).
- If no microorganism is identified, antibiotics should be given for at least 10 to 14 days (3A).

Nosocomial Meningitis

Treatment recommendations for nosocomial meningitis are largely based upon expert opinion. IDSA guidelines for the management of bacterial meningitis recommend vancomycin plus third generation cephalosporin for post-basilar skull fracture meningitis; vancomycin plus cefepime, ceftazidime or merepenem has been recommended for post neurosurgery nosocomial meningitis or meningitis occurring after CSF shunt or penetrating trauma.[603] Meropenem is the preferred option in a setting of infections by extended-spectrum beta-lactamase-producing *Enterobacterales*.[604]

A systematic review of intraventricular or intrathecal use of polymyxins in patients with gram-negative meningitis including 31 case reports and case series found limited available evidence to suggest the addition of intraventricular or intrathecal antimicrobials to systemic therapy in gram-negative meningitis. Toxicity was dose-dependent and reversible.[605] Another review for use of intraventricular use of vancomycin found its use safe and effective.[606] IDSA guidelines recommend vancomycin plus an anti-pseudomonal beta-lactam (such as cefepime, ceftazidime, or meropenem) as empiric antimicrobial of choice for suspected healthcare-associated ventriculitis and meningitis.[607] The current IDSA guidelines suggest using adjunct intraventricular or intrathecal antimicrobial administration if the patient did not clinically improve on solely systemic treatment or the disease is caused by a difficult-to-treat resistant microorganisms. The common drugs include amikacin, colistin and gentamicin. Regarding optimum duration of antibiotic therapy, IDSA recommends therapy for 10 days if coagulase-negative *staphylococcus* or *P. acnes* with no or minimal CSF pleocytosis, normal CSF glucose, and few clinical symptoms or systemic features; 10 to 14 day treatment is recommended in case of significant CSF pleocytosis, CSF hypoglycorrhachia, clinical symptoms or systemic features. Treatment for 21 days is recommended for gram-negative bacilli and *Staphylococcus aureus*. In patients with repeatedly positive CSF cultures on appropriate antimicrobial therapy, IDSA recommends treatment to be continued for 10 to 14 days after the last positive culture.[607] Currently, a single-dose of an antibiotic as per local susceptibility patterns is recommended for prophylaxis.[608,609]

Evidence Statement

Vancomycin in combination with cefepime, ceftazidime or meropenem is a commonly recommended empirical antibiotic regimen for nosocomial meningitis. Alternative regimens include third-generation cephalosporin or meropenem monotherapy or ceftriaxone plus flucloxacillin or cloxacillin combination therapy. Limited available evidence shows the efficacy of intraventricular or intrathecal antibiotics in the management of nosocomial meningitis poorly responsive to systemic antibiotics.

Recommendation

- We recommend vancomycin *plus* cefepime or ceftazidime or meropenem as empirical antibiotics of choice for nosocomial meningitis (3A).
- Colistin may be given if the incidence of CRE or drug-resistant *Acinetobacter* is high in the specific unit (UPP).
- If beta-lactams are contraindicated, we recommend replacing beta-lactam with aztreonam or ciprofloxacin (3A).
- Intraventricular or intrathecal antibiotics should be considered if infection responds poorly to appropriate systemic antibiotics clinically or microbiologically (3A).

What are the Most Common Organisms Causing Brain Abscess in ICU?

Brain abscess is a serious life-threatening emergency with high morbidity and mortality. The management of brain abscess is challenging and needs good clinical and surgical skills for better outcomes. The choice of pharmacological therapy should be based on the most likely organism, patient's predisposing condition or risk factors, mechanisms of infection, antimicrobial susceptibility patterns, and on the ability of the antimicrobial agent to penetrate the abscess.

In a recent single center retrospective study over 62 years including 620 patients of brain abscess, the incidence of brain abscess (per lakhs population) was 2.5 between 1952–1972, 2.6 in 1980–1991 and 2.2 in 2002–2014.[610] *Staphylococcus aureus* is one of the commonest organism followed by Proteus sp. and *Streptococcus*. Chronic ear infection is a common predisposing factor (65% cases).[611] *Streptococcus* (34%), followed by *staphylococcus* (18%), gram-negative enteric bacilli (15%), *pseudomonas* and haemophilus (2% each) were found to be the commonly isolated organisms in a recent meta-analysis. *Peptostreptococcus*, bacteroides and *Fusobacterium* were isolated in 3%, 6% and 2% respectively and polymicrobial etiology was found in 23% cases.[612] Most common predisposing condition was otitis media followed by sinusitis, heart disease, post traumatic, hematogenous, pulmonary disease, postoperative, odontogenic, immunocompromised and meningitis. Two retrospective studies found *Staphylococcus aureus* to be the most common causative organism followed by *Streptococcus*.[613,614] Otitis media was the most common risk factor followed by congenital heart disease, paranasal sinus infections, dental causes, trauma and postoperative state.[613–616] Various prospective Indian studies found *streptococci* to be most common microbe.[615,616]

A recent Indian retrospective study reported that 47.14% samples from brain abscess were culture positive in which 50% had single aerobic/facultative anaerobic bacteria, 30.3% had a mixture of more than one aerobic/facultative anaerobic bacteria, 18.18% had single obligate anaerobic bacteria and 1.5% sample had *Mycobacterium tuberculosis* isolated. Among the total isolates, *Pseudomonas aeruginosa* and *Staphylococcus aureus* predominated.[617]

Evidence Statement

Incidence of brain abscess ranges from 1.3 to 2.6 cases per lakh population. Most commonly involved micro-organisms include *streptococcus* (especially *S. viridans*), *staphylococcus* (especially *S. aureus*), gram-negative bacilli, anaerobes (bacteroides, *Peptostreptococcus*, *Fusobacterium*), *pseudomonas* and *H. influenzae*. Polymicrobial etiology accounts for 23-26% cases. Risk factors include otitis media, sinusitis, head trauma, congenital heart diseases, hematogenous spread, surgery, immunocompromised status, pulmonary disease, meningitis and odontogenic infections.

What are the Empirical Antibiotics of Choice for Treating Brain Abscess in ICU? What should be the Duration of Antibiotic Treatment?

The data regarding the efficacy of various empirical antibiotic regimens in the management of brain abscess is limited to observational studies and expert opinion. In a systematic review and meta-analysis of clinical characteristics and outcomes of brain abscess, 17 studies described how many patients received which regimen.[628]The most common empiric treatment consisted of a third-generation cephalosporin combined with metronidazole, which was given in 53% of cases while vancomycin was added in additional 15% cases. Other regimens had combinations of chloramphenicol, metronidazole with penicillin (9%), ampicillin, gentamicin with metronidazole (9%), and imipenem monotherapy (4%).[612] There is insufficient evidence to make specific recommendations but on the basis of limited clinical data, recommendations include cefotaxime plus metronidazole with or without rifampicin for post-trauma abscess, linezolid or vancomycin plus rifampicin plus meropenem or piperacillin/tazobactam for post-surgical abscess, cefotaxime or piperacillin-tazobactam plus metronidazole for post middle ear, paranasal sinuses, dental causes and cefotaxime with or without metronidazole or ampicillin-sulbactam for cryptogenic or metastatic abscess.[618] Four to six weeks of antibiotic therapy is required for surgically treated abscesses and 6-8 weeks for solely medically treated or multiple surgical abscesses with the largest one treated surgically.[619]

Evidence Statement

The most common empiric treatment consists of a third-generation cephalosporin combined with metronidazole. Antibiotic duration ranges from 4 to 8 weeks.

Recommendation

- We recommend third-generation cephalosporins plus metronidazole as the empirical antibiotic of choice for brain abscess (3A).
- We recommend adding vancomycin if there is a high likelihood of MRSA (3A).
- We recommend vancomycin plus ciprofloxacin if beta-lactams are contraindicated (3A).
- We recommend aztreonam if ciprofloxacin cannot be given or contraindicated (UPP).
- We recommend a minimum 4 weeks of therapy; however, duration may be extended according to clinic-radiological response irrespective of aspiration or excision of abscess (3A).

Skin and Soft Tissue Infections in ICU

An inflammatory microbial invasion of the epidermis, dermis and subcutaneous tissues is defined as skin and soft tissue infection (SSTI). In ICU, 4.3% to 10.5% of septic episodes may be caused by SSTIs,[620] with attributable mortality of 11.7%.[621] Spectrum of SSTI includes abscess, carbuncle, cellulitis, surgical site infection, diabetic foot and necrotizing fasciitis. SSTI has been classified based on signs of sepsis and comorbidities. SSTI without any signs or symptoms of systemic toxicity or comorbidities is termed Class 1. SSTI in patients with significant comorbidities (diabetes or obesity), but without any evidence of sepsis is termed class 2. Class 3 SSTI refers to SSTI with fever, tachycardia and tachypnea with or without hypotension. Class 4 SSTI refers to life threatening infections like necrotizing fasciitis along with sepsis.[622] For treatment decision, it is important to classify SSTIs into purulent (carbuncle, furuncle and abscess) and non-purulent (necrotizing fasciitis, cellulitis and erysipela). Non-purulent SSTIs are classified into mild (no focus of purulence), moderate (presence of systemic inflammatory response syndrome, i.e., SIRS) and severe (failed oral antibiotics, SIRS, immunocompromised, deeper infection or organ dysfunction). Purulent SSTIs are classified into mild (no systemic signs of infection), moderate (SIRS present) and severe (SIRS along with treatment failure, or organ dysfunction).[623]

What are the Most Common Organisms and Risk Factors for SSTI in ICU?

Staphylococcus aureus (20.9%–38.1%) and gram-negative bacilli (29.1%–57.4%) have been commonly implicated in SSTIs in India.[624–626] *Pseudomonas* (11.8%–57.4%) and *E. coli* (17.3%) are most common GNBs.[625,626] High proportion of *Staphylococcus aureus* (40%–74%) have been reported to be methicillin resistant,[625,627] whereas majority of (66.7%–74%) GNBs have been reported to be ESBL producing.[625] Necrotizing fasciitis is caused mostly by *Streptococcus pyogenes* in monomicrobial form. Clostridial species are also responsible for monomicrobial necrotizing fasciitis.[628] In polymicrobial necrotizing fasciitis, the most commonly implicated pathogens are coliforms, anaerobic bacteria and *staphylococcus*.[629,630] Old age, obesity, diabetes mellitus, malignancy, higher APACHE score, longer ICU stay, end stage renal disease, cirrhosis of liver, intravenous drug abuse and neutropenia are risk factors for SSTI.[622,631,632]

Evidence Statement

Older age, diabetes mellitus, obesity, malignancy, cirrhosis and longer ICU stay are risk factors for SSTIs. Gram-positive organisms (*Staphylococcus aureus*) are the most common organism responsible for the SSTIs. *E. coli* and *pseudomonas* are common pathogens among gram-negative organisms. MRSA and ESBL producing gram-negative organisms are the most common causative agents for SSTIs in ICU. Monomicrobial necrotizing fasciitis is commonly caused by *Streptococcus pyogenes*; mixed coliforms, anaerobes and staphylococci are common causes of polymicrobial necrotizing fasciitis.

What are the Empirical Antibiotics of Choice for Treating SSTI in ICU ? For Empirical Therapy, should Combination Therapy be Preferred over Monotherapy?

Studies on SSTIs specific to ICU settings are not available. Meta-analysis performed by Rebecca J et al.[633] showed clear superiority of linezolid and vancomycin in treating skin and soft tissue infection caused by *S. aureus*. Teicoplanin is also a good choice for treating severe SSTI caused by MRSA, with similar efficacy and fewer adverse effects as compared to vancomycin.[634–636] Daptomycin has been shown to have more rapid clinical cure, reduced length of hospital stay and lower cost as compared to vancomycin in a prospective study of SSTIs in ICU.[637] Other RCTs have demonstrated non-inferiority of daptomycin to vancomycin.[638] MRSA remains sensitive to vancomycin and linezolid, and majority remain sensitive to clindamycin also (79%).[627] For gram-negative pathogens, piperacillin-tazobactam and imipenem have been reported to be most effective antibiotics.[620]

Evidence Statement

Vancomycin, teicoplanin, daptomycin and linezolid are effective in SSTIs caused by MRSA. Piperacillin-tazobactam and carbapenems are the most effective antibiotics for ESBL producing gram-negative organisms. Penicillin plus clindamycin are most effective antibiotics in monomicrobial necrotizing fasciitis, whereas a combination of piperacillin-tazobactam, fluoroquinolone and clindamycin is effective for polymicrobial necrotizing fasciitis.

Recommendation

- For moderate non-purulent SSTI, we recommend intravenous penicillin or clindamycin as first choice of antibiotics (2A).
- Severe non-purulent SSTI should be treated with a combination of piperacillin-tazobactam along with coverage for MRSA (vancomycin, teicoplanin, daptomycin or linezolid) (2A).
- Concomitant surgical inspection or debridement should be considered for severe non-purulent SSTIs (2A).
- For severe purulent SSTI, incision and drainage followed by empiric antibiotics including piperacillin tazobactam, along with MRSA coverage (vancomycin, teicoplanin, daptomycin or linezolid) is recommended (3A).
- Penicillin plus clindamycin is recommended for monomicrobial necrotizing infection caused by *Streptococcus pyogenes* or clostridial species. For polymicrobial necrotizing fasciitis, a combination of piperacillin-tazobactam, fluoroquinolone and clindamycin is recommended (3A).

What should be the Duration of Antibiotic Treatment for SSTI?

There is limited literature to guide treatment of severe or complicated SSTIs. In uncomplicated SSTI, antimicrobial administration for 5 days was equally effective to 10 day treatment.[639] Complicated SSTIs may require longer treatment.

Evidence Statement

Shorter course of antibiotic therapy is adequate for uncomplicated SSTIs while complicated SSTIs require longer duration of antibiotic therapy.

Recommendation

- Severe nonpurulent SSTIs should be treated with at least 5 days of antibiotics (3A).
- Severe SSTIs with organ dysfunction should be treated with a prolonged course of antibiotics of 2-3 weeks duration (3A).

Sepsis of Unknown Cause in ICU

Mortality from severe sepsis and septic shock remains consistently high.[640,641] Delay in antimicrobial therapy is associated with increased in-hospital and overall mortality in severe sepsis and septic shock.[642,643] In view of this data, empiric antimicrobial therapy should be started immediately (preferably within 1 hour) after presumptive clinical diagnosis of septic shock. While every effort should be made to secure site-specific cultures to guide microorganism-specific therapy, this should never delay the administration of empiric antimicrobials.[644] Intensive efforts, including imaging, should be undertaken in an attempt to evaluate the source of infection. Two sets of blood cultures and other appropriate microbiological specimens should preferably be taken before empirical therapy. Urgent empirical broad-spectrum coverage to include all common pathogens should be administered.[644]

What is the Empirical Treatment for Sepsis of Unknown Cause in ICU?

There is paucity of data on empirical antimicrobial therapy in sepsis of unknown cause in ICU. Combination antimicrobial therapy (using two drugs from different class) improves survival and clinical outcomes in patients with sepsis who are critically ill and in septic shock as compared to monotherapy.[645] Beta-lactams with aminoglycosides or fluoroquinolones gives a broad empirical coverage. If the patient has risk factors for MRSA, vancomycin should be added to the regimen.[646] Accordingly if risk factors for MDR pathogens are present in an individual patient, beta-lactam of choice is a carbapenem. In India, empirical therapy should cover for various tropical infections till a definite diagnosis is reached. Third-generation cephalosporins with doxycycline is an appropriate option keeping this fact in mind.

Evidence Statement

Empirical therapy with dual class (with different mechanisms of action) combination antimicrobial therapy for sepsis of unknown cause in ICU is associated with have better clinical outcomes. Empirical therapy with either piperacillin-tazobactam or carbapenems in combination with aminoglycoside or fluoroquinolone has been shown to give appropriate broad coverage leading to better clinical outcomes as compared to monotherapy.

Recommendation

- We recommend empirical antimicrobial therapy with combination of ceftriaxone and doxycycline or macrolide for community-acquired sepsis of unknown origin in ICU (UPP).
- We recommend empirical antimicrobial therapy with combination of beta-lactam/beta-lactamase inhibitor and fluoroquinolone or aminoglycoside for nosocomial sepsis of unknown origin in ICU (UPP).
- Empiric therapy should attempt to provide antimicrobial activity against the most likely pathogens based upon clinical features along with local patterns of infection and resistance (UPP).
- Duration of therapy is 7 to 10 days, though longer courses may be appropriate in patients with slow response (3B).

Empirical Antifungals for Non-neutropenic Patients in ICU

Invasive fungal infection (IFI) is an important cause of morbidity and mortality among critically ill patients. Early institution of antifungal therapy is pivotal for mortality reduction. Starting targeted antifungal therapy after culture positivity or identification of pathogen requires a long time. Therefore, alternative strategies (defined as untargeted antifungal treatment) for antifungal therapy institution in patients without proven microbiological evidence of fungal infections have been considered.[647] Untargeted antifungal strategies include prophylactic antifungals, pre-emptive antifungals and empirical antifungals. Prophylaxis refers to use of antifungals without proven or suspected fungal infection but with risk factors for its development. Pre-emptive (diagnosis driven) approach means evidence of fungal infection, without definitive microbiological proof on the basis of surrogate biomarkers like 1-3 ß-D-glucan, mannan or anti-mannan antibodies, whereas empirical(fever-driven) approach refers to using antifungals in patients at risk for IFI, with signs and symptoms of infection, in absence of microbiological evidence of infection.[647]

Among fungal pathogens, *Candida* spp. are the most commonly isolated microorganisms, currently being the fourth most commonly identified pathogens in nosocomial BSIs and the third most common pathogens isolated in ICU patients.[307] Despite advances in antifungal therapy, the mortality associated with invasive candidiasis remains as high as 40%.[647] In India, incidence of C. albicans ranges from 34% to 45.6 % with an attributable mortality of 20% to 35.6%. Incidence of non-albicans *Candida* is on the rise with attributable mortality ranging from 23% to 52%, with higher mortality associated with *Candida* krusei.[648] An observational study from Indian ICUs revealed an incidence of 6.5 cases per 1000 ICU admissions. There was a high prevalence of *C. tropicalis* (41.6%) and 46.6% isolates were susceptible to all antifungals. Fluconazole resistance was 5.2% for C. albicans while it was 2.6% for *Candida* tropicalis. Risk factors for invasive candidemia were found to be surgery especially abdominal surgery, central venous catheters, invasive mechanical ventilation, urinary catheterization, hemodialysis and total parenteral nutrition.[328]

What are the Risk Factors for Invasive Fungal Infections in ICU?

Risk factors for invasive fungal infections (IFIs) in ICU have been studied extensively. A large retrospective study in 301 surgical ICU patients found the risk factors for IFI to be peripheral and central intravenous catheters, bladder catheters, mechanical ventilation, lack of enteral nutrition and TPN.[649] In a prospective study of 150 cardiothoracic ICU patients, risk factors for IFIs were prolonged mechanical ventilation (>10 days), hospital-acquired bacterial infection, cardiopulmonary bypass duration greater than 120 min, diabetes mellitus and high APACHE II score (>30).[650] A systematic review demonstrated that major surgery (OR-7.3), TPN (OR-3.8), fungal colonization with colonization index >0.5 (OR-19.1), hemodialysis (OR-3.8), acute renal failure (OR-4.2), severe sepsis, mechanical ventilation >3 days, diabetes (OR-2.8), APACHE 2 score >16 (OR-1.03), cardiopulmonary bypass >120 min (OR-8.1), use of broad-spectrum antibiotics (OR-3), red cell transfusion and central or peripheral venous catheters were significantly associated with IFIs.[651]

Evidence Statement

Risk factors for invasive fungal infections in non-neutropenic patients in ICU are surgery, total parenteral nutrition, renal replacement therapy, cardiopulmonary bypass >120 minutes, diabetes mellitus, central venous catheters, urinary catheters, *Candida* colonization with colonization index >0.5, use of broad-spectrum antibiotics, acute renal failure, mechanical ventilation >3 days and APACHE II score >16.

What is the Role of Empirical Antifungals in Non-neutropenic Patients in ICU?

The advantage of empirical antifungal treatment has already been established in high-risk patients such as cancer patients and solid organ transplant recipients in various studies.[652–654] However, in non-neutropenic critically ill patients, the definitive evidence for efficacy of untargeted treatment in terms of prevention of IFIs or mortality benefit has been equivocal. Moreover, studies have shown potential detrimental effects of the injudicious use of antifungal agents in the form of emergence of drug resistance, side effects and financial costs.[655–657] Several randomized controlled trials have compared empirical antifungals to placebo in non- neutropenic critically ill patients.[658–663] In a RCT including post-surgery patients, fluconazole reduced the occurrence of candidemia (5.8% in fluconazole vs 16% in placebo) though the mortality rates were similar.[658] Similarly, use of caspofungin was also associated with trend towards decreased IFI without any difference in mortality or length of hospital stay.[660] A systematic review demonstrated that although empirical antifungals in non-neutropenic patients in ICU reduced the incidence of subsequent IFI, it had no impact on mortality.[663] In a randomized controlled trial involving 260 mechanically ventilated patients with *Candida* colonization, empirical micafungin administration reduced the rate of subsequent proven IFI (12% vs 3%; $p = 0.008$) without any significant mortality benefit.[662]

Evidence Statement

Empirical antifungals for non-neutropenic patients in ICU routinely has not been associated with decrease in mortality or hospital length of stay. Empirical antifungals in patients at high risk for invasive fungal infections in ICU has been shown to reduce incidence of subsequent proven invasive fungal infections.

Recommendation

- We do not recommend the routine use of empirical antifungals in non-neutropenic patients in ICU (1A).
- Empirical antifungals may be considered in critically ill patients with high risk of invasive fungal infections to reduce the incidence of subsequent invasive fungal infections (1B).

What is the Antifungal Agent of Choice and Duration of Empirical Therapy in Non-neutropenic Patients in ICU?

The options for antifungal therapy include fluconazole, amphotericin-B and echinocandins. In a systematic review, empirical use of fluconazole and caspofungin reduced rates of subsequent IFI while micafungin, nystatin and amphotericin-B did not.[663] No direct comparative data of efficacy of different antifungals for empirical therapy in non- neutropenic patients in ICU is available. Indian studies have shown increasing prevalence of non-albicans *Candida* with high rates of fluconazole resistance in the range of 5% to 7%.[664] Regarding duration of empirical antifungal therapy, there are no studies directly comparing different duration

of empirical antifungal therapy. Most of the studies have used at least 2 weeks therapy.[663]

Evidence Statement

Fluconazole and caspofungin are useful as empirical antifungal therapy in non-neutropenic ICU patients at high risk of Invasive fungal infection. In India, rate of fluconazole resistance is up to 7%, especially in non-albicans *Candida* species.

Recommendation

- We recommend fluconazole or caspofungin as preferred empirical antifungal agents in non- neutropenic ICU patients at risk for invasive fungal infection (1A).
- Caspofungin may be preferred in areas with high prevalence of fluconazole resistance (1B).
- Micafungin or anidulafungin may be used as alternative agents (3A).
- Recommended duration of empirical antifungal therapy is 2 weeks (3A).

Antibiotic Stewardship

Antibiotic stewardship program is defined as "coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting the selection of the optimal drug regimen including dosing, duration of therapy, and route of administration."[665] An efficient antibiotic stewardship program results in optimum clinical outcomes while reducing adverse effects of unnecessary antibiotic use. Every additional 10 days of antibiotic therapy conferred a 3% increased risk of an adverse drug event. These adverse effects include emergence of antibiotic resistance, *clostridium difficile* infections and drug toxicity and occurs in 20% of patients.[666] A structured antibiotic stewardship program requires a multidisciplinary approach. Core elements of antibiotic stewardship program includes committed leadership, accountability, expertise in drugs, action, tracking drug resistance patterns, regular reporting and education to clinicians about optimal prescribing.[667]

Does Antibiotic Stewardship Improve Patient Outcome in ICU?

Antibiotic stewardship programs reduced duration of antibiotic treatment (1.95 days; 95% CI, 2.22 to 1.67) and duration of hospital stay (1.12 days, 95% CI, 0.7- 1.54) without any significant difference in mortality in a recent systematic review.[667] In a recent meta- analysis, there was reduced mortality with guideline directed empirical therapy (RR 0.65, 95% CI, 0.54- 0.80, $p < 0.0001$) and antibiotic de-escalation (RR 0.44, 0.30- 0.66).[668] Mortality benefit has also been reported in another systematic review (RR 0.68, 95% CI, 0.52-0.88).[669] However, a single non blinded randomized study showed significantly higher rate of superinfection with de-escalation of antibiotics as compared to continuation of empirical therapy (27% vs 11%; $p = 0.03$).[670]

Evidence Statement

Antibiotic stewardship programs in hospitalized patients are associated with reduction in number of antibiotic days, duration of hospital stay and all-cause mortality.

Recommendation

All hospitals should have an antibiotic stewardship program including the intensive care units (1A).

What are the Essential Strategies of Antibiotic Stewardship in an ICU Setting?

Prospective audit-feedback and Preauthorization are commonly used strategies of antibiotic stewardship.[671–673] In prospective audit and feedback, treating clinicians are provided recommendations regarding appropriateness of antibiotics used. Advantages of this strategy include avoidance of delay in antibiotic administration (as physician is engaged after prescription of antibiotics). Limitations of this strategy include partial compliance (due to voluntary participation of physicians), resource intensive nature, and longer lag period for visible benefits to become apparent. Prospective audit and feedback strategy resulted in reduction in utilisation of antibiotics and significant cost reduction.[674–675] In a systematic review, enabling strategies including feedback resulted in greater efficacy of stewardship interventions.[671] Preauthorization, another strategy of antibiotic stewardship, requires approval by concerned authority before starting antibiotics.[672] This affects use of restricted antibiotics only and may result in potential delay in antibiotic initiation. Without feedback, this may also result in increased use of other antibiotics and hence lead to selection of different resistance patterns. However, it provides immediate results in terms of recued antibiotic usage. Other potential drawbacks include development of negative professional culture because of breakdown in communication between infectious disease specialists and clinical teams.[671] Enabling and restrictive strategies have been compared in a quasi-experimental crossover trial using days of antibiotic therapy in both strategies.[676] In this study involving 2,686 patients in pre-prescription authorization (PPA) group and 2,693 patients in post prescription review with feedback (PPRF) group, initially antibiotic days of treatment (DOT) remained relatively unchanged in the PPA arm. When changed to the PPRF arm, antibiotic use decreased (-2.45 DOT per 1000 patient-days [PD]) hence concluding that PPRF may have more impact on decreasing days of antibiotic therapy.

In another quasi-experimental study comparing both strategies in 55336 patients, after the introduction of prospective audit with feedback, both total antimicrobial use (+9.65 DOT/1,000-PD per month; $p < 0.001$) and broad-spectrum anti-gram-negative antimicrobial use (+4.80 DOT/1,000-PD per month; $p < 0.001$) increased significantly as compared to preauthorization in the pre intervention period.[677] Use of cefepime and piperacillin-tazobactam both significantly increased after the intervention ($p = 0.03$). Hospital LOS and LOS after first antimicrobial dose also significantly increased after the intervention ($p = 0.016$ and 0.004, respectively).

Evidence Statement

Antibiotic stewardship requires a multidisciplinary approach with integration of infectious disease physician, microbiologist with logistic and financial support from hospital administration. Both enablement and restrictive strategies are useful in improving adherence to antibiotic stewardship programs. Restrictive strategies give immediate results. Enablement practices are more resource intensive. Most studies have used a combination of both the methods and have shown additive effects. Providing feedback to the treating team improves adherence. A single RCT has shown that restrictive strategy alone may cause delay in initiation of antibiotics.

Recommendation

Prospective audit of antibiotic use and/or preauthorization (if feasible) along with feedback to the treating team is recommended as part of antibiotic stewardship program (1A).

What is the Role of Antibiotic Cycling, Intravenous to Oral Switch and De-escalation in the ICU?

Antibiotic cycling refers to withdrawing a specific antibiotic or an antibiotic class from use for a definite period of time and substituting with another antibiotic or antibiotic class having a similar spectrum of activity.[672] This is postulated to induce different resistance mechanisms in the microorganisms and hence prevent or reverse the development of antibiotic resistance. There is no compelling evidence on the benefit of antibiotic cycling in terms of clinical end points. Several prospective before and after studies without control groups have demonstrated reduction in incidence of ventilator-associated *pneumoniae* (6.7% with antibiotic cycling as against 11.6% before the intervention)[678] as well as reduction in colonization.[678–680] A newer prospective cohort study[681] comparing antibiotic mixing and antibiotic cycling found no significant differences in infection rates (16.6% and 14.5%, OR 0.9), infection due to target microorganisms (5.9% and 5.2%, OR 0.9), hospital length of stay (median 5 days for both groups) or in hospital mortality (13.9% and 14.3%, OR 1.03).

Evidence Statement

Antibiotic cycling in the intensive care unit has not been adequately studied in randomized controlled trials. Non-randomized studies show significant heterogeneity in terms of site of study, method of cycling and confounders like simultaneous infection control measures being employed. Evidence of benefit of antibiotic cycling is lacking, with few studies demonstrating reduction in colonization though mortality and length of hospital stay remain unchanged.

Recommendation

Antibiotic cycling should not be used as a method of antibiotic stewardship program (2A).

Scheduled Intravenous to Oral Switch

Timely switch from intravenous to oral antibiotics has been shown to reduce cost of health care and length of hospital stay.[682–687] In case of antibiotics with availability of equivalent oral formulations, the scheduled switch is easier than in case of broad-spectrum antibiotics without oral formulations or precise like piperacillin tazobactam or meropenem. A multicenter randomized controlled trial done in CAP which evaluated scheduled switch to oral antibiotics after 2 days of intravenous antibiotics found similar cure rates, survival or resolution of chest radiology with significantly lower total cost of care (2953$ and 5002$, $p < 0.05$).[686] Oosterheert et al.[685] also found similar results when comparing scheduled switch on day 3 and day 7 with similar cure rates and mortality rates in both groups but with significantly reduced duration of intravenous antibiotics and hospital stay, with differences of 3.4 days and 1.9 days respectively.

Evidence Statement

Early intravenous to oral transition of antibiotics reduce hospital length of stay and cost of care. There is no increase in mortality or other adverse events when this is done after assessing as to which patients can be safely transitioned to oral therapy.

Recommendation

Antibiotic stewardship programs should implement strategies to improve timely transition from parenteral to oral antibiotic therapy (2A).

De-escalation in Intensive Care Unit

Antibiotic de-escalation refers to a strategy of switching from broad-spectrum antimicrobials to a narrower spectrum of antimicrobials. It is recommended to reduce emergence of multidrug-resistant bacteria as well as costs of health care. In a multicenter randomized controlled trial, de-escalation was associated with longer ICU stay but similar in hospital mortality in severe sepsis.[670] In a recent meta-analysis of 9 studies involving 1,873 patients with septic shock, de-escalation of antibiotics was associated with trend towards reduced mortality (RR 0.74, 95% CI, 0.54- 1.03).[688] In another systematic review, de-escalation was associated with lower mortality (RR 0.68; 95% CI, 0.52–0.88).[669]

Evidence Statement

Pooled results from observational studies in an ICU setting do not show any increase in mortality with antibiotic de-escalation while significantly reducing antibiotic exposure days and ICU length of stay.

Recommendation

Antibiotic de-escalation in the ICU is recommended as part of antibiotic stewardship program (2A).

What is the Role of Procalcitonin in Antibiotic De-escalation in ICU?

Procalcitonin is a 116 amino acid precursor to calcitonin. Normal serum or plasma levels of procalcitonin in healthy adults are <0.05 ng/mL. It can be produced by a variety of cell types in response to inflammatory stimuli, especially of bacterial origin. It does not usually rise significantly in response to viral or non-infectious inflammation and so has the potential to be used as a marker of bacterial infection. The levels in serum is quantified using immunoassay.[284] Procalcitonin use to guide antibiotic therapy in sepsis in intensive care unit resulted in reduction in antibiotic days (MD –3.19 days, 95% CI, –5.44 to –0.95) duration of hospital stay (MD –3.85 days, 95% CI, –6.78 –0.92) as well as a trend towards reduction in duration of ICU stay (MD –2.03 days, 95% CI, –4.19 to 0.13 days).[689] Procalcitonin guided algorithm for antibiotic discontinuation (decrease by >80% of peak value, or <0.5 ng/mL) led to reduced antibiotic administration (between-group absolute difference 1.22, 0.65–1.78, $p < 0.0001$), with significant mortality benefit (20 vs 25%; between-group absolute difference 5.4%, 95% CI, 1.2–9.5, $p = 0.0122$).[115] In a recent Cochrane meta-analysis involving 26 trials, procalcitonin utilisation for antibiotic discontinuation was associated with reduced mortality (adjusted OR 0.83, 95% CI, 0.70 to 0.99, $p = 0.037$).[118]

Evidence Statement

Implementation of antibiotic de-escalation algorithm based on serial procalcitonin measurements has been shown to reduce mortality, length of ICU stay, total duration of antibiotic days and health care costs.

Recommendation

Procalcitonin based algorithms may be used for antibiotic de-escalation (1A).

Antimicrobial Prescription in Critically Ill Immunocompromised Patients

Advances in ICU care of immunocompromised patients have resulted in improved and meaningful survival rates.[690] Early intensive care can be used to treat reversible causes of acute worsening in patients with advanced malignancy.[691] Patients with primary immunodeficiencies are increasingly being recognised. However, more often, patients without a prior diagnosis present with severe sepsis and septic shock in the intensive care unit where careful clinical assessment and high index of suspicion can lead to diagnosis of the underlying immunodeficiency.[692] This separate yet heterogenous group of immunocompromised patients present different challenges to the intensive care physician due to febrile neutropenia, increased risk of bloodstream infections, invasive fungal infections and other complex issues which have led to separate guidelines for this group.[693–695]

The Febrile Neutropenic Patient

Febrile neutropenia (FN) is defined as an oral temperature of >38.3°C or two consecutive readings of >38.0°C for 2 h and an absolute neutrophil count (ANC) of $<0.5 \times 10^9$/L or expected to fall below 0.5×10^9/L.[693] These guidelines are applicable in a critically ill febrile neutropenic patient presenting to the ICU with any of the following clinical or laboratory parameters of organ failure but not limited to

- Hypotension.
- Tachypnea requiring oxygen therapy more than 4 liters/min to maintain saturation >90%.
- Altered mental status (without focal neurological deficit).
- Oliguria or rising serum creatinine.

What should be the Empiric Antibiotic Therapy in Critically Ill Febrile Neutropenic Patients with Suspected Bloodstream Infection?

In India, in febrile neutropenic patients, gram-negative bacteremia is much more common than gram-positive bacteremia (Table 3); in contrast to the western data, where gram-positive isolates are more common.[694,695] The spectrum of bacterial isolates from number of studies in India suggest *Enterobacter*iaceae (*E. coli* and *Klebsiella* species) and *Pseudomonas aeruginosa* to be the most common among gram-negative organisms. Among gram-positive isolates, *Staphylococcus aureus* and Coagulase negative *staphylococcus* are most common isolates (Table 3).[696–703]

There is scarce data regarding the choice of empirical antibiotic regimens in critically ill febrile neutropenic presenting to the Indian ICUs. Most of the studies have heterogeneous patient population—leukemia, lymphoma, solid tumors etc. Choice of antibiotics depends on most likely causative microorganism as per the local isolate patterns, clinical focus of infection, host and disease characteristics, local antimicrobial sensitivity patterns, and mechanism of action of antimicrobials (bacteriostatic/bactericidal). Recent data shows increased prevalence of MDR organisms. Several studies in India have shown that majority of gram-negative bacteria isolated on initial blood cultures from patients were resistant to the non-carbapenem first-line antibiotics.[704–707] Hence, initial antibiotic choice in a febrile neutropenic patient who is critically ill presenting to the ICU will be carbapenems like Meropenem or Imipenem. The prevalence of carbapenem resistant gram-negative organisms is alarming at present. According to ICMR data on non-neutropenic population, carbapenem resistance among *Enterobacter*iaceae is 35-50 %, *Pseudomonas* spp 47% and *Acinetobacter* spp 62%.[707] Based on the epidemiology, current evidence and clinical experience the

Table 3: Isolates from blood of febrile neutropenic patients in India

Author, year	*No. of isolates*	*Gram-negative isolates (%)*	*Common organisms (%)*	*Gram-positive isolates (%)*	*Common organisms (%)*
Prabhash K et al.[696] 2010	484	68.1	*Pseudomonas* 30.37, *Acinetobacter* 11.57 *E. coli* 10.9 *Klebsiella* 7.23 Enterococcal spp. 4.13	31.9	Staph Aureus- 12.6(MRSA- 2) Cons-10.5 *Streptococcus* spp. 4.55 *Burkholderia* spp. 2.89 *Enterobacter* spp. 2.27
Karanwal et al.[697] 2013	23	78	*E. coli* 43, *Pseudomonas* 17.47	22	Staph aureus 22 CONS- 4
Singh et al.[698] 2014	693	74.6	*E. coli* 23.5, *Pseudomonas* 6.7	25.4	Staph Aureus- 34(MRSA 13) Enterococcus 29
Rajendranath R et al.[699] 2014	40	58.3	*E. coli* 36.7, *Pseudomonas* 9.2	41.7	Staph aureus- 25 (MRSA- 2.5)
Sengar M et al.[700] 2014	739	66	*E. coli* 19, *Pseudomonas* 18.7 *Acinetobacter* 7.1 *Enterobacter* 4.8	34	Cons-20 Staph aureus- 5.5 *Streptococcus* 3.9 Enterococcus 3.6
Lakshmaiah KC et al.[701] 2014	92 (11 positive)	61.7	*E. coli* 36	38.3	Staph Aureus- 36(MRSA 9)
Vivek B et al.[702] 2016	285	63	*Pseudomonas* 22 *E. coli* 21.4	37	CONS 12.9 Staph Aureus 8
Sevitha Bhat et al.[703] 2021	306 (blood –46 patients)	69.9	*Klebsiella* spp-18.3 *Pseudomonas* spp -17.6 *E. coli*-14.7%	30.1	Staph aureus -13.7

committee has identified risk factors for carbapenem resistance. Particular subgroups of patients, such as acute leukemia patients presenting to the ICU, patient already on carbapenem shifted to ICU from ward, previous multidrug-resistant infections in the last 1 month and patients on vasopressors are at risk of harboring carbapenem resistant organisms.[708] Hence in these groups of patients, initial empiric antibiotic regimen should include *colistin*/polymyxin B along with meropenem.[707]

Vancomycin is not a standard part of empirical antibiotic therapy for febrile neutropenic patient. In the western countries with predominant gram-positive bacteremia and high incidence of MRSA, studies have failed to show any benefit with empiric vancomycin in terms of fever or mortality.[709] In India, with predominant gram-negative sepsis and low incidence of MRSA-35%.[707] Vancomycin or Teicoplanin is recommended as part of initial antibiotic regimen only in patients with suspected indwelling catheter infection (rigors following infusion, cellulitis at exit site), skin and soft tissue infection, severe mucositis, culture growing gram-positive cocci pending identification, previous MRSA colonization/infection and hemodynamic instability admitted from home/OPD.[696]

Evidence Statement

Gram-positive and gram-negative organisms are common causes of febrile neutropenia, with gram-negative organisms predominating in India. The commonly isolated GNBs include *Enterobacter*iaceae (*E. coli* and *Klebsiella* species) and *Pseudomonas aeruginosa* to be the most common among gram-negative organisms. *Staphylococcus aureus* and Coagulase negative *staphylococcus* are most common gram-positive isolates. Recent studies have reported increasing prevalence of MDR organisms. Choice of antibiotics depends local epidemiology, focus of infection and host and disease characteristics. Current evidence shows carbapenem resistance among *Enterobacter*iaceae is 35–50%, *Pseudomonas* spp. 47% and *Acinetobacter* spp. 62%. Acute leukemia patients presenting to the ICU, patient already on carbapenem shifted to ICU from ward, previous multidrug-resistant infections in the last 1 month and patients on vasopressors are at risk of harboring carbapenem resistant organisms. Empiric upfront vancomycin has not been shown to improve clinical outcomes or mortality in febrile neutropenia. Patients at risk of MRSA infections include suspected indwelling catheter infection (rigors following infusion, cellulitis at exit site), skin and soft tissue infection, severe mucositis, culture growing gram-positive cocci pending identification, previous MRSA colonization/ infection and hemodynamic instability at admission.

Recommendation

- In a critically ill febrile neutropenic patient presenting to the ICU with organ failure, empiric antibiotic therapy should be initiated with or escalated to a broad-spectrum carbapenem like imipenem or meropenem (UPP).
- Empiric combination of Meropenem and Colistin/Polymyxin B should be considered in patients having high risk of infection with resistant gram-negative organisms (3A). Following risk factors should be assessed:
  - Critically Ill patients with underlying acute leukemia (on induction or consolidation therapy) presenting to the ICU.
  - Patients of acute leukemia/lymphomas on beta-lactam/beta lactamase inhibitor± aminoglycosides, shifted to ICU from ward.
  - Previous history of infection with multidrug-resistant organism in last 1 month.
  - Hypotensive patients requiring vasopressor infusions (refractory septic shock).
  - Patient shifted to the ICU on carbapenem therapy.
- We strongly caution against the use of empiric combination of Meropenem and Colistin/Polymyxin B or Colistin/Polymyxin B alone in patients who are not high risk of infection with carbapenem resistant gram-negative organisms as defined above (3A).
- We caution against use of other carbapenems like Doripenem and Ertapenem due to lack of positive evidence and inadequate spectrum respectively (2A).
- Vancomycin/Teicoplanin should be added as empiric therapy in critically ill febrile neutropenic patient with risk factors for MRSA infection (3A). These include:
  - Suspected indwelling vascular catheter infection.
  - Skin and soft-tissue infection.
  - Previous colonization/infection with methicillin-resistant *Staphylococcus aureus*.
  - Blood Culture growing gram-positive cocci awaiting identification.
  - Severe mucositis.
  - Hemodynamic instability(hypotension) at admission from home or outpatient department (UPP).
- Empiric MRSA coverage should be avoided in absence of risk factors for MRSA and in ICUs with low prevalence of MRSA (UPP).
- After the initiation of empiric therapy based on the factors listed above, the subsequent therapy should be based on the organisms isolated and sensitivity patterns. In patients with no isolates, the treatment should be continued as per the response to ongoing antibiotics and appearance of any new focus of infection (UPP).

What Methods should be Used for Early Identification of Causative Organisms in Febrile Neutropenia Patients?

Blood cultures are an important investigation in all patients with sepsis requiring ICU admission.[710] However, the method of sample collection is associated with improved yield. With the advent of modern point of care tests like multiplex PCR, early isolation of causative organism can lead to early institution of appropriate antimicrobial therapy. Volume of blood is an important variable for detection of bloodstream infection volume of blood. Each mL of blood increased the yield (detection of positive culture) of blood cultures in adults by approximately 3%. Collection of two blood culture sets prior to antibiotic administration provide 30% yield of bloodstream pathogens in critically ill patients.[711] In pediatric population, smaller volumes of blood are suggested due to lesser total blood volume. Consensus is not to exceed 1% of a patient's total blood volume. Use of BioFire Blood Culture Identification 2 panel for pathogen identification has shown pooled specificity of >97% and pooled sensitivity was 92.3–98.2% for the common organisms as compared to the culture-based methods. This could guide early treatment for multidrug-resistant organisms.[341] Their utility in Indian scenario has not been proven with high quality studies.

Evidence Statement

Two sets of blood cultures drawn prior to antibiotic administration yields microbiologic diagnosis in 30% cases. Addition of multiplex PCR techniques can aid in early diagnosis and has high sensitivity and specificity as compared to culture-based methods.

Recommendation

- We recommend collection of at least 2 sets of blood cultures, with a set collected simultaneously from peripheral site and one central. In case of multi lumen catheter, one set per lumen should be collected (1A).
- Two blood culture sets from separate veneipunctures should be sent if no central venous catheter is present (1A).
- One set includes one aerobic and one anaerobic culture bottle. Blood culture volume should be at least 10 mL/bottle (1A).
- The use of molecular methods for identification of multidrug-resistant organisms and their antibiotic sensitivity pattern can be considered in critically ill patients, however, the availability and cost may be a concern along with risk of false negativity and false positivity (2B).

What should be the Approach to Empiric Antifungal Therapy in Febrile Neutropenia in Critically Ill Immunocompromised Patients?

Invasive *Candida* or *Aspergillus* infections have been demonstrated in the autopsy of patients who died of neutropenic fever with no clinical evidence of invasive fungal infection (IFI) except for a continuous fever.[712] It is estimated that approximately 15–45% of patients with prolonged neutropenia have invasive fungal infection (IFI). IFI is difficult to diagnose both in critically ill patients and in patients with febrile neutropenia. Invasive fungal infection is associated with high mortality in both these groups especially if treatment is delayed.[713–716] Invasive aspergillosis should be suspected in patients with persistent febrile neutropenia with the development of signs of *pneumoniae* including lung infiltrate.[695] There is limited evidence for antifungal prophylaxis in febrile neutropenia to prevent *Candida* infections.[714,717–719] High-risk patients who have received intensive cytotoxic chemotherapy are at risk for invasive fungal infection. Yeast (primarily *Candida* species) and molds typically cause infections, which are manifested by persistent or recurrent fever in patients with prolonged neutropenia, rather than causing initial fever in the course of neutropenia. Empirical antifungal therapy is instituted for the treatment of "occult" fungal infection presenting as persistent neutropenic fever despite 4–7 days of empirical antibiotic therapy, however, early initiation may be needed in critically ill patients with risk factors for the invasive fungal infections.[719] Poor sensitivity of chest radiograph compared to CT scan for detection of *pneumoniae* in this population should be kept in mind.[34] The galactomannan assay is highly specific for *Aspergillus* species with some cross-reactivity with *Histoplasma capsulatum* and Penicillium species. False-positive reaction can occur with concomitant use of b-lactam/b-lactamase combinations, such as piperacillin/tazobactam, however, false positivity rates are considerably lower with newer generation assays.[720,721] Bronchoalveolar lavage (BAL) galactomannan had sensitivity of 0.88 and a specificity of 0.81 in immunocompromised patients if standard cut-off of 0.5 optical density (OD) was used, in a recent meta-analysis. Increasing the limit to OD> 1 led to sensitivity of 0.78 and a specificity of 0.93.[722] Use of Beta-D Glucan (BDG) alone has limited sensitivity for the diagnosis of invasive candidiasis.[723] However, BDG had good sensitivity 76.8% (95% CI, 67.1–84.3%), and specificity (85.3, 95% CI, 79.6–89.7%) for differentiating probable or proven IFI from no IFI.[734] Pre-emptive antifungal therapy for invasive fungal infections is a strategy which involves serial screening of high risk patients for fungal colonization using biomarkers like beta-D-glucan, galactomannan and imaging (CT Chest) and initiation of treatment if either imaging or serology shows any evidence of an invasive fungal infection.[695,725] This approach is useful in patients who develop febrile neutropenia on antifungal prophylaxis with suspicion is for an invasive mould infection. Pre-emptive antifungal therapy was similar in terms of all-cause mortality in febrile patients with mixed population of cancer and post-transplant (HSCT) patients.[726] A RCT of 549 AML and MDS patients undergoing induction chemotherapy or allogeneic HCT had similar survival with empiric and pre-emptive caspofungin.[727]

Amphotericin B has been most commonly prescribed as empiric antifungal therapy in febrile neutropenia, Due to similar efficacy and lesser toxicity, liposomal formulations are preferred over deoxycholate.[728] Caspofungin was found to have similar overall success rates when compared to liposomal amphotericin B in an RCT of 1,095 patients with febrile neutropenia.[729] It is generally agreed upon that individual echinocandins namely caspofungin, micafungin and anidulafungin have similar efficacy and are interchangeable.[730] Other echinocandins (micafungin, anidulafungin, and rezafungin) have limited data for febrile neutropenia. The echinocandins have demonstrated significant fungicidal activity and treatment success against most of the *Candida* species in randomized clinical trials. Availability of intravenous formulation, limited drug interactions, favorable safety and efficacy profile make them the first choice of empirical antifungal in critically ill patients including patients with febrile neutropenia. Caspofungin (loading dose 70 mg followed by 50 mg daily) needs dose adjustment for moderate to severe hepatic dysfunction whereas micafungin and anidulafungin do not need dose adjustments in liver or renal failure. Echinocandins do not provide coverage against *cryptococcus*, trichosporon and non-*aspergillus* filamentous molds like fusarium, endemic fungi.[731] As echinocandins have poor penetration in eye, CNS, and urine, they should not be used for treatment of fungal meningitis, endophthalmitis and urinary tract infection. Echinocandins have shown to be effective in salvage therapy however they are not recommended as monotherapy for the primary treatment of IA due to lack of evidence.[719]

Voriconazole could not achieve its primary endpoint of noninferiority when compared to liposomal amphotericin in 837 patients with febrile neutropenia and persistent fever, though voriconazole group had fewer breakthrough fungal infection (2% vs 5%), and had lesser adverse events.[732] Voriconazole remains an option in febrile neutropenia due to spectrum of activity against *Candida* and *aspergillus* species.[695] Posaconazole has not been studied for febrile neutropenia. Posaconazole is noninferior for treatment of invasive aspergillosis,[733] whereas Isavuconazole is efficacious in treatment of invasive aspergillosis and mucormycosis.[734] Isavuconazole was inferior in treatment of invasive candidiasis and candidemiasis.[735] Though itraconazole has been studied in febrile neutropenia, it is not preferred due to lack of common availability of intravenous preparations, variable bioavailability of oral preparations, negative inotropic properties and safety concerns in patients with renal or hepatic dysfunction.[736]

Lipid formulations of amphotericin B should be used as first-line treatment if Mucormycosis (Zygomycosis) is suspected. Recommended dose is 3–5 mg/kg daily.[728] Amphotericin B deoxycholate should be avoided in patients with underlying renal impairment, patients on other nephrotoxic drugs such as cyclosporine or tacrolimus after allogeneic HSCT, or antibiotics, such as aminoglycosides and in patients with previous history of toxicity. Voriconazole can be used for suspected or proven cases of invasive pulmonary aspergillosis. Dose of Voriconazole is 400 mg (6 mg/kg) twice daily for 2 doses, then 4 mg/kg) twice daily. As mentioned above, Echinocandins are recommended for salvage therapy of aspergillosis.[719]

Recommended minimum duration of therapy for candidemia without metastatic complications is 2 weeks after documented clearance of *Candida* from the bloodstream, provided neutropenia and symptoms attributable to candidemia have resolved.[695] Recommended duration of invasive pulmonary aspergillosis is 6–12 weeks based on the resolution of symptoms and neutropenia.[725]

Combination antifungal treatments are used with the rationale to maximize treatment by targeting multiple sites or metabolic pathways or different steps in the same pathway hence leading to an additive or synergistic effect. While *in vitro* studies on combination antifungals showed additive or synergistic effect; in vivo studies have given mixed results. Marr et al. demonstrated 8.2% absolute reduction in mortality rates with the combination of voriconazole and anidulafungin in adult patients with hematologic malignancies (HMs) and hematopoietic cell transplantation (HCT) having probable or proven Invasive aspergillosis. However, this difference was not statistically significant.[737]

Evidence Summary

Patients with febrile neutropenia are at risk of developing invasive fungal infections. IFIs have high mortality in patients with febrile neutropenia. Persistent or recurrent febrile neutropenia and development of lung infiltrates may be clues to fungal etiology of febrile neutropenia. Yeast (primarily *Candida* species) and molds are common etiologic agents. In patients with persisting fever without any localization, empiric antifungals targeting *Candida* species are initiated. Chest radiograph has poor sensitivity for *pneumoniae* detection in patients with febrile neutropenia, and CT Chest is preferred. Galactomannan assay is highly specific for *Aspergillus* species with some cross-reactivity with *Histoplasma capsulatum* and Penicillium species. False-positive reaction can occur with concomitant use of b-lactam/b-lactamase combinations, such as piperacillin/ tazobactam. Use of Beta-D Glucan alone has limited sensitivity for the diagnosis of invasive candidiasis. Invasive aspergillosis should be suspected in patients with persistent febrile neutropenia with the development of signs of *pneumoniae* including lung infiltrate.

The echinocandins have demonstrated significant fungicidal activity and treatment success against most of the *Candida* species in randomized clinical trials. Individual echinocandins namely caspofungin, micafungin and anidulafungin have similar efficacy and are interchangeable. Echinocandins have poor penetration in eye, CNS, and urine. Echinocandins are not active against Zygomycosis. Voriconazole is the preferred agent for invasive aspergillosis, whereas liposomal amphotericin B is preferred for zygomycosis. Echinocandins have been useful in salvage therapy of aspergillosis. Guidelines advise to continue treatment for candidemia for at least two weeks after 2 weeks after documented clearance of *Candida* from the bloodstream, and resolution of neutropenia and symptoms attributable to candidemia. Recommended duration of invasive pulmonary aspergillosis is 6–12 weeks based on the resolution of symptoms and neutropenia. Combination antifungal treatments have limited evidence for added efficacy.

Recommendation

- Following patients should be considered for initiation of antifungal therapy when they present to ICU with shock or respiratory distress especially when they have persistent or recurrent fever or clinical deterioration after >3 days of broad-spectrum antibiotics (2A).
  - Allogenic HSCT.
  - Severe mucositis with diarrhea.
  - Prolonged/anticipated duration of neutropenia >10 days.
  - Worsening on broad-spectrum antibiotics like BL/BLI and Carbapenems.
  - More than 2 weeks of high-dose steroids (more than 15–20 mg of prednisolone or equivalent).
  - History of invasive fungal infection.
  - New onset lung infiltrate. (Since chest x ray has low sensitivity, HRCT should be done in these patients).
- We recommend the use of caspofungin (echinocandin group) as initial antifungal therapy. Caspofungin should be avoided in patients with chronic liver disease (Child-Pugh C) (2A).
- Anidulafungin and Micafungin can be considered if there are contraindications to use of caspofungin (3A).
- Voriconazole is the drug of choice for proven, probable or possible aspergillosis. Due to its variable bioavailability voriconazole should be administered IV. In patients with renal dysfunction caspofungin can be given instead of IV voriconazole (1A).
- Liposomal Amphotericin B is the drug of choice for suspected or confirmed Mucormycosis (1A).
- All efforts should be made to confirm presence of invasive fungal infection with the use of tests including CT Chest/ suspected site (abdomen for hepatosplenic candidiasis or mucormycosis/paranasal sinus for mucormycosis), β–D-glucan, serum and BAL Galactomannan, fungal culture. Tissue (lung/ other clinically involved sites) biopsy should be performed if required, whenever feasible and safe (1A).
- We do not recommend routine use of combination antifungal therapy for probable or proven Invasive aspergillosis (IA) due to lack of strong evidence (3A).

Which Patients Empiric Treatment Against *Pneumocystis jirovecii Pneumoniae*?

Patients considered high risk for PCP infection are allogeneic HSCT recipients, autologous HSCT, high-dose corticosteroid therapy and patients receiving T-cell-depleting agents such as fludarabine, purine analogues and rituximab.[738–740] Hypoxemia is the most characteristic abnormality in PCP *pneumoniae*. Chest radiograph might be normal in early disease. Though most patients with hematologic malignancies and chemotherapy receive prophylaxis for *pneumocystis jirovecii* infection,[741] acute onset hypoxemic respiratory failure, or characteristic radiologic infiltrates should prompt empiric initiation of sulfamethoxazole/trimethoprim.

Evidence Statement

HSCT, high dose corticosteroids, T-cell depleting agents and rituximab predispose to PCP infection. Hypoxemia and characteristic radiologic abnormalities indicate PCP *pneumoniae*, though chest radiograph might be normal in early disease. Empiric treatment with trimethoprim-sulfamethoxazole is indicated in suspected PCP *pneumoniae*.

Recommendations

- Treatment with sulfamethoxazole/trimethoprim should be considered in high risk patients such as allogenic HSCT, high-dose corticosteroid therapy administration of T-cell-depleting agents such as fludarabine/purine analogues and rituximab when such patients present with hypoxemic respiratory failure with or without radiological evidence of Pneumocystis carinii *pneumoniae* especially if they are not on PCP prophylaxis (3A).
- Every attempt should be made to confirm PCP infection (3A).

What is the Role of Empiric Antiviral Therapy in Immunocompromised Patients with Febrile Neutropenia?

Respiratory syncytial virus and parainfluenza are important co-pathogens causing upper and lower respiratory tract infections, especially in post hematopoietic stem cell transplantation. These infections lead to increased risk of mortality. Although aerosolized and oral administration of ribavirin has been used, there is no antiviral agent proven to be effective against parainfluenza virus. There is no clear evidence from randomized trials that aerosolized or oral ribavirin or any other antiviral is effective against RSV *pneumoniae*.[742–745]

Evidence Statement

Antiviral therapy in febrile neutropenia is given according to treatment guidelines of the etiologic agent. There are no effective agents for treatment of parainfluenza and respiratory syncytial virus infection at present.

Recommendations

- There is no role of empirical antiviral therapy with febrile neutropenia. Active HSV or VZV infections in neutropenic patients indicated by clinical or laboratory evidence should be treated with Acyclovir (3A).
- Immunoglobulin tests should not be used to diagnose VZV or HSV infection (3A).
- Ganciclovir is recommended for the empiric therapy for CMV in patients with high risk of CMV reactivation (3A):
  - Administration of T-cell-depleting agents such as fludarabine/purine analogues, rituximab.
  - Patients on high dose steroids who develop diarrhea.
  - *Pneumoniae* not responding to antibiotics & antifungals.
- No specific treatment for infections with RSV and parainfluenza viruses due to lack of specific evidence (3A).

What is the Role for Empiric Antimicrobial Therapy for Tropical Infections like Malaria, Leptospirosis in Patients with Febrile Neutropenia?

There are occasional reports of malaria in patients on chemotherapy with solid tumor and hematolymphoid malignancies with febrile neutropenia. In a series of 99 patients of acute leukemia on chemotherapy with febrile neutropenia, malaria was responsible for fever in only 4% of patients.[746]

Febrile Neutropenia patient presenting to ICU often have thrombocytopenia due to disease itself, chemotherapy or sepsis. Presence of fever and thrombocytopenia itself should not warrant empirical anti-malarial therapy even in malaria endemic country like India.

A high-index of suspicion is warranted in a resident or traveler of malaria endemic area who presents with the classic triad of symptoms (fever, chills and sweating). If malaria is suspected, peripheral smear for malaria parasite and rapid malaria antigen (histidine-rich protein II (HRP-II) antigen of Plasmodium falciparum and common Plasmodium lactate dehydrogenase (pLDH) of Plasmodium species should be performed early and antimalarial therapy should be initiated in positive cases. With rapidity (diagnosis in less than an hour) and good negative predictive value of (98.2 %) malaria antigen test, antimalarial therapy is restricted only to positive cases.[747]

There is lack of enough evidence documenting etiological role of other tropical infections like Leptospirosis in subset of patients with febrile neutropenia; hence we believe that until enough evidence is available, suspected or documented tropical infections in neutropenic patients in ICU should be treated similar as they are treated in non-neutropenic patients.

Evidence Statement

There is insufficient evidence regarding tropical infections in patients with hematologic or solid organ malignancies and febrile neutropenia.

Recommendation

- There is no role for empirical antimicrobial therapy against tropical infections like malaria, leptospirosis in febrile neutropenia patients (3A).
- Documented tropical infections in neutropenic patients in ICU should be treated similar as they are treated in non-neutropenic patients (UPP).

What is the Role of Surveillance Cultures in Guiding Therapy in Febrile Neutropenia Patients?

As most of the infections in neutropenic patients occur due to organisms in respiratory or gastrointestinal tract, therefore surveillance culture seems to be a reasonable strategy in deciding the empiric antibiotic therapy in febrile neutropenia. The studies published in 1980's and 90's supported the practice of surveillance culture. However there has been a very poor correlation between blood and fecal isolates in most of the studies.[748,749]

Widespread antimicrobial treatment may inhibit the growth or distort the proportion of different species found in Fecal cultures. A recent study conducted in pediatric allogeneic HSCT patients has demonstrated a positive predictive value of 0.9% to bacterial surveillance cultures, with a sensitivity of 33.3% and a specificity of 47.4%. Surveillance cultures were not cost effective. The sampling and analyses require lots of laboratory and nursing resources.[750] Another study in adults who got admitted for HSCT concluded that surveillance blood cultures in patients who have undergone HSCT do not identify bloodstream infections. The number of positive blood cultures was not helpful in determining which patients had infection.[751]

Evidence Statement

Surveillance cultures have not been shown to correlate with subsequent causative organisms in immunocompromised patients.

Recommendation

- We strongly recommend against repeated surveillance cultures as these do not help to guide antibiotic therapy (3A).

What is the Role of Source Control in the Treatment of a Febrile Neutropenic Patient?

Control of source in the form of drainage of an abscess, debridement of infected necrotic tissue and removal of a potentially infected device is of paramount importance. Foci of infection readily amenable to source control include but not limited to intra-abdominal abscesses, gastrointestinal perforation, ischemic bowel or volvulus, cholangitis, cholecystitis, pyelonephritis associated with obstruction or abscess, necrotizing soft tissue infection, empyema, septic arthritis and implanted device infections. There is general agreement that source control should be done at the earliest to reduce microbiological burden and mere antibiotics and resuscitation would not achieve cure unless adequate source control is done. If Vascular catheters are suspected, its prompt removal should be considered. It is important to note that the classical clinical signs of infection (rubor, calor, dolor etc.) be absent due to low neutrophil counts.[710]

Evidence Statement

Source control at the earliest possible time reduces microbiologic burden and improves outcomes. Source control includes debridement, drainage of collections, removal of incriminated indwelling catheters and implanted devices.

Recommendations

We recommend that in patients with febrile neutropenia with clinically documented source of infection (as defined below), immediate intervention should be undertaken for source control (3A).

What Should be the Approach to Antibiotic De-escalation in Patients with Febrile Neutropenia?

Data on de-escalation strategies in neutropenic patients after identification of a clinically relevant pathogen is scant but there is no data on de-escalation when no pathogen has been identified. Although antibiotics are required to treat an occult infection during neutropenia, marrow recovery is necessary to protect the patient.[18]Shorter duration of antibiotics have been shown to have equal efficacy to longer courses (7–14 days) in various ICU infections including CAP and VAP.[167,174] However, most stewardship trials have excluded immunocompromised patients. In leukemia, discontinuation of empiric antibiotics have been advised in hemodynamically stable patients who remain afebrile for 72 hours.[708] Early discontinuation (72 hours) of antibiotics was noninferior to extended antibiotic therapy (afebrile for 5 days, of till recovery of neutrophils) in an open label RCT of 281 patients with febrile neutropenia after chemotherapy of hematopoietic stem cell transplantation. However, there was higher adverse events (16% vs 10%) and greater mortality (3% vs 1%), which was due to patients who continued to remain febrile.[752]

Evidence Statement

Antibiotic de-escalation to definitive therapy is feasible after identification of causative organism or in patients who remain afebrile for >48 hours with evidence of marrow recovery.

Recommendations

Antibiotic de-escalation should be considered in the following situations (3A):

- Once and if a pathogen is identified, we recommend de-escalation to an antibiotic that the organism is susceptible to.
- Treat with appropriate agents based on the site and pathogen until the patient is afebrile for at least 48 hours and there is evidence of marrow recovery (neutrophil count ≥500 cells/mm^3).
- In patients without microbiologically documented infection continue empirical antimicrobials until the patient is afebrile for at least 48 hours and there is evidence of marrow recovery (neutrophil count ≥500 cells/mm^3).

Which Antibiotics Should be Used for Febrile Neutropenia due to Multidrug-resistant Bacteria?

If MRSA is suspected or isolated, Vancomycin, teicoplanin, linezolid and daptomycin are the available options. Linezolid and daptomycin are effective against vancomycin-resistant enterococci. However, daptomycin cannot be used in cases with *pneumoniae*. For ESBL producing GNBs carbapenems are efficacious. However, carbapenemase producing *Klebsiella* need to be treated with colistin or tigecycline.[695] Combination therapy of piperacillin tazobactam with tigecycline had high success rate (68% vs 44%) in an open-label trial of 390 high-risk patients with hematologic malignancies. More than 30% of GNB isolates were piperacillin-tazobactam resistant.[753] Other antibiotics with efficacy against MDR GNBs include fosfomycin, but have limited evidence.[754]

Evidence Statement

Antibiotics like fosfomycin, tigecycline and minocycline have activity against variety of MDR gram-negative organisms. For MRSA, vancomycin, teicoplanin and linezolid have most evidence. Linezolid is effective against vancomycin-resistant enterococci. However, good quality RCTs for MDR infections are lacking in immunocompromised patients.

Recommendation

- Antibiotics like Fosfomycin, tigecycline and minocycline may be considered in infection with multidrug-resistant bacteria in presence of *in vitro* susceptibility after considering the in vivo penetration at source of sepsis, and if alternate agents with proven efficacy are not available or contraindicated (3A).
- Vancomycin or linezolid can be used in cases of MRSA (1A).

Antimicrobial Guidelines in Solid Organ Transplant Recipients

Infectious complications in solid organ transplant (SOT) recipients admitted to intensive care unit (ICU) pose a challenge with respect to both diagnosis and treatment. The epidemiological exposures of the recipient as well as the donor and the net immunological state of the recipients determine the risk of infection in them.[755,756] The latter incorporates an assessment of several important contributing factors like[755,757]

- Pretransplant diagnosis or treatment.
- Specific organ transplanted (e.g., lung/kidney vs liver transplant).
- Intraoperative events like cold ischemia time, severity of shock or need for blood/ blood product transfusion, duration of surgery.
- Choice of induction and maintenance immunosuppression.
- Comorbidities (e.g., viral co-infection [hepatitis C virus (HCV), cytomegalovirus (CMV)], malnutrition, end-organ failure [cirrhosis, chronic kidney disease]).
- Breach of the mucocutaneous barrier: Indwelling devices, mucositis.
- Need for extracorporeal therapies.

These patients may not mount typical symptoms and signs of infection like fever or any localizing signs, so a high index of suspicion for infection and detailed assessment is required. The infections in SOT patients can be categorized as follows:

C–Community-acquired
R–Reactivation
E–Epidemiologic exposure
D–Donor-derived
I–Iatrogenic
T–Travel related

It is advisable to have a syndrome-based approach (e.g., Nonspecific febrile illness, *pneumoniae*, urinary tract, central nervous system) at first and then narrow the differential diagnoses of possible organisms that could cause the clinical presentation(s).

Microbiological diagnosis is crucial in this patient group. In the context of extensive differential diagnoses, the value of early and specific diagnostics with the use of invasive procedures if necessary (bronchoscopy, tissue biopsy, or aspiration of collections) to obtain specimens cannot be underestimated. After transplantation, serologic techniques are of limited use because transplant recipients may not mount timely serologic responses. Thus, antigen detection or molecular nucleic acid detection assays are preferred over serologic testing.

What are the Common Infections in Post Solid Organ Transplant Patients? What Should be the Preferred Approach to Empiric Therapy and Diagnostic Evaluation?

The timeline of post-transplant infections can be used to establish a differential diagnosis for infectious syndromes at various stages after transplantation (Table 4).[755–757] Infections occurring outside the usual period or of unusual severity suggest excessive immunosuppression or epidemiologic hazard. Most centers use a variation of standard 'triple immunosuppression' (prednisone, calcineurin inhibitor, antimetabolite such as mycophenolate mofetil).

Incidence of sepsis in SOT recipients ranges between 20% to 60% and is associated with in-hospital mortality ranging between 5% to 40%.[758] The infections in the first month posttransplant are usually of nosocomial origin, opportunistic infections predominantly till around 6 months and after that community-acquired infections are the predominant ones. During the first month after SOT, opportunistic infections are generally absent as the full effect of immunosuppression has not yet been established. The common infections in this period are of nosocomial origin, donor or recipient derived, related to surgical/technical issues and indwelling catheters.[755,756] Most of these infections are of bacterial followed by fungal etiology. In a study by Ram et al. in post renal transplant patients, urinary tract infection (UTI) followed by line related infections were the most common in the first moth after transplant. Ram et al. reported that 23.6% of the SOT recipients develop UTI during first 4 weeks and *E. coli* was the most common causative agent (12.6%). CMV was the most common (prevalence of CMV 21.8%) between 4 weeks to 3 months after renal transplantation and could cause allograft loss. Tuberculosis reactivation was more common between 3 months to 1-year post-transplant (prevalence of tuberculosis being 10.6%). Pneumocystis carinii and *Aspergillus* infection usually occurred after 1 year.[759]

Kumar et al.[760] and Sriperumbuduri et al.[761] also found UTI to be the most common infection in the post renal transplant patients. Neelima et al. studied the microbiological profile of transplant (SOT and hematopoetic stem cell transplant - HSCT) recipients in a south Indian center and found UTI to be the most common infection (53.3%) followed by bloodstream infection (BSI) (21.6%). Of all the bacterial isolates, 81.6% were gram-negative, 18.4% gram-positive, *E. coli* being the predominant one (52.5%). In 38.77% drug resistance was observed and of them 68.4% were multidrug-resistant (MDR).[762] Al-Hasan et al. found that the incidence of gram-negative BSI was highest in the first month post SOT (210.3/1000 person-years) which sharply declined to 25.7 per 1000 person-years between 2 and 12 months. Most of GNB BSI was nosocomial (27.4%) or healthcare associated (49.8%), remaining being community-acquired. For 55.2% of gram-negative BSI, urinary tract was the primary source follows by gastro-intestinal tract, respiratory tract, intravascular catheters, skin-soft tissue in that order.[763] *Escherichia coli* accounted for 36.8% of gram-negative BSI followed by *Klebsiella pneumoniaee* (14.3%), *Pseudomonas aeruginosa* (13.0%), *Enterobacter* cloacae and *Citrobacter* freundii in that order. *Pseudomonas aeruginosa* was the most common isolate in the first month post SOT, while *E. coli* and K. *pneumoniae* were more common 12 months post SOT.

In a prospective Swiss Transplant Cohort Study (STCS) studying the burden and timeline of post SOT infections in the first year postoperatively in 3,541 patients, the authors reported that 1,520 patients (55%) suffered 3,520 infections. 63% of the infections were caused by bacteria, *Enterobacter*iaceae being the predominant ones (54%) as urinary pathogens in heart, lung, and renal transplant recipients, and as digestive tract pathogens in liver transplant recipients. Enterococcus was found to be responsible for 20% of infections (as urinary tract pathogens in renal transplant recipients and as digestive tract pathogens in liver transplant recipients) and *Pseudomonas aeruginosa* was the isolated pathogen (9%) in lung transplant recipients. Herpes virus was the predominant viral pathogen among the 1,039 viral infections in post renal, cardiac and liver transplant patients. *Candida* species accounted for 60% of the 263 fungal infections. Opportunistic infections including *Aspergillus* and CMV were rare (1.4% and 6% respectively), spread throughout the year.[764]

In a systematic review and meta-analysis conducted by Green et al.,[765] they reported that 25 to 45% of kidney transplant recipients develop UTI in immediate postoperative period, out of which around 50% were related to urinary catheters. The incidence of UTI increased to up to 70% in first 6 months post-transplant. Enteric gram-negative bacteria and Enterococci were the most common pathogens, with the resistant strains (e.g., extended spectrum beta-lactamase-positive *Escherichia coli*, carbapenem-resistant *Klebsiella pneumoniaee*) becoming more frequent. They reported that the risk for developing sepsis with bacteremia was lowered by 87%, and the risk for developing bacteriuria (symptomatic or asymptomatic)

Table 4: Timeline of infections post solid organ transplant (SOT)

	0–1 month post SOT	*1–6 months post SOT*	*>6 months post SOT*
Infection characteristics	• Nosocomial infection- pneumonia/ UTI/ bloodstream infection • MDRO infection • Post-surgical/surgical site infection • Indwelling device related infection- CRBSI/ CAUTI • Donor derived infection • Recipient colonization related infection (e.g., *Aspergillus*, *Pseudomonas*)	• Opportunistic infection • Re-activation of latent infection	• Community-acquired infection (usually): pneumonia/ UTI • Chronic or recurrent infection with stereotypical organisms in specific subsets • Re-activation of latent infection in presence prolonged immunosuppression
Common responsible organisms			
Bacteria	• MDR organisms MRSA VRE MDR GNB • *Clostridium difficile* associated infection • *Pseudomonas/Burkholderia* spp. in Cystic fibrosis: lung tr	• *Mycobacterium tuberculosis* • Listeria • *Legionella* • *Nocardia* • *Clostridium difficil* colitis • Gram-negative enteric bacilli in Small bowel transplant • *Pseudomonas/Burkholderia* spp. in Cystic fibrosis-lung transplant	• Ongoing risk of M. tuberculosis, Listeria, *Legionella*, *Nocardia* if immunosuppression continued • Nontuberculous *mycobacteria* • Community-acquired pathogens: *S pneumoniae, H influenzae,* M catarrhalis, S aureus, *Mycoplasma pneumoniae*, Chlamydia *pneumoniae*
Viruses	• HSV (in absence of anti-HSV prophylaxis) • HIV • West Nile virus	• CMV, EBV, HSV, VZV (if not on prophylaxis) • HCV reactivation • RSV, Adenovirus • BK polyoma virus	• Recurrent HSV, VZV • Adenovirus • RSV • HCV Reactivation • Late-onset CMV (colitis, retinitis), • EBV related PTLD
Fungi	• Candida (likely to be Fluconazole resistant) • Early Aspergillosis (Uncommon, possible due to recipient colonization)	• *Aspergillus* • *Cryptococcus neoformans* • *Pneumocystis jirovecii* (if not on prophylaxis)	• During intense immunosuppression: • *Aspergillus* (more so in Lung transplants with chronic rejection) • *Cryptococcus* • Mucor, atypical molds • *Pneumocystis jirovecii*
Parasites	Rare	• *Toxoplasma* gondii • Strongyloides • Leishmania • Trypanosoma cruzi	• Ongoing risk of *Toxoplasma*, Strongyloides, Leishmania, Trypanosoma, if immunosuppression intensified

MDRO, multidrug-resistant organism; UTI, urinary tract infection; CRBSI, catheter related blood stream infection; CAUTI, catheter associated urinary tract infection; MRSA, methicillin resistant *Staphylococcus aureus*; VRE, vancomycin resistant enterococcus; GNB, gram negative bacteria; HSV, herpes simplex virus; VZV, varicella zoster virus; CMV, cytomegalovirus; EBV, Epstein Barr virus; HIV, human immunodeficiency virus; RSV, respiratory syncytial virus; HCV, hepatitis C virus; PTLD, Post-transplant lymphoproliferative disorder

by 60% by initiating prophylaxis in these patients. However they couldn't find any difference in incidence of all cause mortality or graft survival with or without prophylaxis. This study was limited by the small number of trials evaluating the efficacy and outcome related to prophylaxis.

Depending upon the organ transplanted, the local epidemiological factors, and the local antibiogram, the anti-infective surgical prophylaxis should be prescribed. Antimicrobial coverage for skin flora, *enterobacteri*aceae, biliary enterococcus species, anaerobes is usually prescribed for liver transplant patients. Similarly for lung transplant patients, the prophylaxis is usually targeted against molds, gram-negative bacteria or usual colonizer patterns.[755] For example, the patients undergoing lung transplant for cystic fibrosis often are colonized with MDR bacteria (*Pseudomonas aeruginosa* most commonly, in up to 52% pre-transplant; *Burkholderia*, *Stenotrophomonas maltophilia* and Achromobacter being the less frequent ones in that order) in the pre-transplant period. Early postoperative prophylaxis should be initiated/modified depending on donor and recipient bronchial cultures.[766]

TMP-SMX as primary prophylaxis for UTI in post-renal transplant patients (given for PJP prophylaxis) has been found to decrease UTI and bacteremia. If TMP-SMX cannot be used as primary prophylaxis, other agents like nitrofurantoin, cephalexin or fluoroquinolone (ciprofloxacin/ ofloxacin) may be used in high risk patients or those having recurrent UTI in the preoperative period, and in this case limited to first month after transplant.[767] Fluoroquinolones should only be used with special caution.[768] Their use for primary prophylaxis has been linked to increase in fluoroquinolone resistant *Pseudomonas aeruginosa*.[767]

The incidence of opportunistic infections have decreased owing to anti-infective prophylaxis.[756,757] The patterns of opportunistic

infections also have altered because of anti-CMV strategies and TMP-SMX prophylaxis. TMP-SMX prophylaxis provides protection not just against *Pneumocystis jirovecii pneumoniae*, but also against *Toxoplasma gondi*i infection and has been proven to decrease incidence of UTI, *Listeria monocytogenes* meningitis, and *Nocardia* infections.[755]

As the immunosuppression is progressively reduced after 6 months, the prophylaxis against the opportunistic infections should also be withdrawn. However, it can be re-introduced in case of intensified immunosuppression, wherever indicated.[757]

Evidence Statement

Incidence of sepsis in solid organ recipients ranges from 20% to 60% and is associated with in-hospital mortality of 5% to 40%. Nosocomial infections predominate in the first month, opportunistic infections till six months posttransplant and subsequently community-acquired infections become most common. Most of these infections are of bacterial followed by fungal etiology. Most common site remains urinary tract infection, followed by line related infections, and *E. coli* the most common etiology. CMV is most common infection from 1 month up to 3 months, whereas tuberculosis reactivation is more common from 3 months to 1 year posttransplantation. Pneumocystis and *aspergillus* infections are common after 1 year. MDR GNB isolates are increasing in prevalence, especially in nosocomial infections. Risk for developing sepsis with bacteremia can be lowered significantly by antibiotic prophylaxis. Prophylaxis is governed by type of transplant and risk of specific infections. Liver transplant patients often receive antibiotics covering skin flora, *enterobacter*iaceae, enterococci and anaerobes whereas post-lung transplant, prophylaxis is against molds, gram-negative bacteria or colonizers. Post-kidney transplantation trimethoprim-sulfamethoxazole given for PJP prophylaxis reduces UTI and bacteremia. Alternatives include nitrofurantoin and cephalexin. Fluoroquinolone increase risk of resistant infections like *pseudomonas*, and should be used with caution. Opportunistic infections have decreased due to anti-infective prophylaxis for CMV and PJP. TMP-SMX provides protection against *toxoplasma*, and protects against UTI, *Listeria* meningitis and *nocardia*l infections.

Recommendation

Anti-infective Prophylaxis

- Prophylaxis in first month posttransplant should depend upon the nosocomial infections, colonization of donor and recipient, and the organ transplanted (1A).
- Trimethoprim-sulfamethoxazole (TMP-SMX) for primary prophylaxis for urinary tract infection (UTI) in renal transplant patients is recommended; TMP-SMX usually given for 6 months for PJP prophylaxis decreases UTI and bacteremia in renal transplant recipients (1A).
- Primary prophylaxis for UTI with agents other than TMP-SMX may be limited to the first month after transplant (3B).

Approach to Diagnosis and Treatment of Infection

- Infections in the first month (0–30 days) of post SOT period should be investigated and treated similarly to those of non-immunocompromised postoperative patient (1A).
- Infections in the first month (0–30 days) of post SOT period should be investigated and treated on the lines of nosocomial infections/ donor derived infections (1A).
- Complete blood count with differential, liver and renal function tests, serum electrolytes should be obtained in all patients with suspected infection (3A).
- We recommend obtaining blood cultures at presentation and preferably prior to initiation of antibiotics in all patients presenting with features suggestive of infection (3A).
- Antimicrobials should be administered considering prior cultures, local antibiogram and susceptibility patterns (1A).
- Asymptomatic bacteriuria (AB) should not be treated (1A) unless same pathogen has been isolated twice consecutively >105 CFU/mL in first 2 months post SOT (2B) or AB is found in Post-kidney transplant recipients (1B).
- Multidrug-resistant (MDR) urinary tract infection (UTI) with gram-negative bacteria such as *Pseudomonas* spp and *Klebsiella* spp, newer agents like ceftazidime-avibactam can be considered as alternatives to colistin or aminoglycosides (1B).

Approach to Diagnosis and Treatment of Respiratory Infection

Acute respiratory failure (ARF) following SOT could be of infectious or non-infectious etiologies such as *pneumoniae*, pulmonary edema, alveolar hemorrhage, primary graft dysfunction (PGD)/ rejection, acute respiratory distress syndrome (ARDS), pleural effusion.[757,768] Chest radiograph should be obtained in all patents with ARF as it may help in narrowing down the differential diagnosis.[769] Consolidation may be observed in bacterial infection or pulmonary hemorrhage, diffuse interstitial infiltrates are usually suggestive of *pneumoniae* (due to CMV, *Pneumocystis jirovecii*, respiratory viruses, EBV, *mycoplasma*, *Legionella* etc.) or other non-infectious etiologies like alveolar hemorrhage, pulmonary edema, graft rejection, ARDS.[757,769,770] Ground glass pattern or ground glassing along with micro nodular infiltrates could suggest PJP or CMV *pneumoniae*.[769,771]

Broncho*pneumoniae* or peribronchial opacities maybe observed in infection due to *Chlamydia*, *Mycoplasma*, Haemophilus, *Neisseri*a, respiratory viruses. Nodular infiltrates (single/ multiple) may suggest invasive mold (aspergillosis), *Nocardia*, TB, non-tuberculous *mycobacteria* infections or possibility of malignancy/ PTLD.[769,771]

Obtaining appropriate routine microbiologic cultures before starting antimicrobial therapy in patients suspected of having sepsis or septic shock, without causing a delay in start of treatment, was recommended as a best practice statement in Surviving Sepsis Guidelines (SSC) 2016 and remained valid in SSC 2021 guidelines.[772,773]

In a prospective multi center study, incidence of *pneumoniae* was found to be 10.1 episodes/1000 recipients/year and in 70.4% of cases it was classified as late-onset *pneumoniae* (>6 months post SOT). In 94.4% of patients, an attempt to obtain a microbiological diagnosis was made and diagnostic yield was reported to be 60.7%.[774]

In an active population-based surveillance for community-acquired *pneumoniae* requiring hospitalization among adults, the authors found that among 2,259 patients who had radiographic evidence of *pneumoniae* and specimens available for both bacterial and viral testing, a pathogen was detected in 853 (38%): one or more viruses in 530 (23%), bacteria in 247 (11%), bacterial and viral pathogens in 59 (3%), and a fungal or *mycobacteria*l pathogen in 17 (1%). They concluded that despite current diagnostic tests, no pathogen was detected in the majority of patients.[61] In another prospective study of 610 kidney transplant recipients, of the 60 episodes of *pneumoniae* in 54 patients (8.8%), 23 (38%) were of nosocomial origin and rest were community-acquired infections. Bacterial infection was the most common, followed by fungal and

viral (44%, 7%, and 3.5% respectively). *P. aeruginosa was t*he most common microorganism isolated in nosocomial *pneumoniae* (26%), among which 50% were multidrug-resistant). No microorganism was isolated in 34% episodes. Among community-acquired *pneumoniae*s *S. pneumoniaee* (11%) was the most common pathogen. No microbiologic confirmation of disease was made in 54% of cases. The overall accuracy of bronchoalveolar lavage (BAL) was found to be 72%. The authors concluded that nosocomial pulmonary infections were associated with considerable morbidity and mortality in kidney transplant recipients and that carrying out invasive procedures for the diagnosis of *pneumoniae* is useful.[775]

Performance of BAL in SOT recipients with *pneumoniae* provides a moderate chance to come to a microbiological diagnosis, performed with or without transbronchial biopsy, the microbiological yield of BAL ranging from 39% to 77% in various studies (highest yield reported in nosocomial *pneumoniae*).[769] Different studies have studied performance of lung biopsy for diagnosis of lung infiltrates in SOT patients. The diagnostic yield of open lung biopsy was reported to be 85.1% in a single center study on renal transplant patients with resultant change in therapeutic management in 53% of patients. However, complications were reported in 28.7%.[776] The diagnostic yield of percutaneous CT guided lung biopsy in a series of 45 biopsies in SOT patients with parenchymal lung nodules was reported to be 53%, with complications in 13% of patients.[777] The decision for performance of lung biopsy should be left to clinician's discretion and be individualized per patient depending on the risk -benefit ratio.[769]

Empiric antimicrobial therapy for *pneumoniae* in SOT patients would depend upon the net state of immunosuppression, the epidemiological exposures, the clinical and radiological profile of the patient, and the local antibiogram. The usual empiric coverage doesn't include antifungals, or coverage for invasive and opportunistic infections; this gap in antimicrobial coverage should always be borne in mind.

Evidence Statement

Acute respiratory failure (ARF) following SOT can be due to variety of infective and noninfective causes. Patterns of involvement on chest radiograph or CT scan can help to narrow down diagnosis. Ground glass opacities and micronodular infiltrates can suggest PJP or CMV, whereas lobar consolidation suggests bacterial etiology. Nodular infiltrates suggest fungal, tubercular or malignant etiology. Majority of cases of community-acquired *pneumoniae* have been seen after 6 months posttransplantation. Early initiation of antibiotics after sending blood cultures in patients with septic shock leads to better outcomes. Organisms responsible for CAP include viruses, bacteria, fungal and *mycobacteria*. *Streptococcus pneumoniaee* has been reported to be most common bacteria causing CAP, whereas *P. aeruginosa* was the most common microorganism isolated in nosocomial *pneumoniae*. Bronchoscopic BAL leads to microbiologic diagnosis in up to 77% cases. CT Guided biopsy has been used for diagnosis of patients with lung nodules. Open lung biopsy has been reported to have high yield (85%) but with increased risk of complications. Empiric antimicrobial therapy for *pneumoniae* in SOT patients would depend upon the net state of immunosuppression, the epidemiological exposures, the clinical and radiological profile of the patient, and the local antibiogram.

Recommendation

- We recommend obtaining chest radiograph in all patients with suspected *pneumoniae* (2A).
- We recommend performing a chest computerized tomography (CT) scan in all SOT patients with *pneumoniae* (I, A) and high resolution CT (HRCT) scan in patients with nodular infiltrates with suspected invasive aspergillosis (1A).
- We recommend obtaining nasopharyngeal swab for influenza virus testing by PCR if seasonally appropriate and high suspicion for viral *pneumoniae*(1A).
- Early BAL should be considered in SOT patients with suspected *pneumoniae* admitting to ICU (1A).
- We recommend BAL in patients with pulmonary infiltrates not improving on empiric antimicrobial therapy or in whom there is diagnostic uncertainty on non-invasive testing (1A).
  - BAL fluid should be tested for:
    - Stains and immunohistochemistry: Gram stain, KOH/ Calcofluor white, Auramine-rhodamine, Auramine-O, or Ziehl-Neelsen, Modified acid-fast stain, Silver methenamine stain, Galactomannan assay (<0.5 Negative predictive value, >3 positive predictive value)
    - Polymerase chain reaction (PCR): *Mycobacterium tuberculosis* (Cartridge Based Nucleic Acid Amplification Test (CB-NAAT or GeneXpert), Multiplex PCR assay [(Including Respiratory viruses, CMV)(Quantitative or semiquantitative detection-particularly bacterial)].
    - Culture: Aerobic culture for bacteria, *mycobacteria*l growth indicator tube (MGIT) for *Mycobacterium tuberculosis*, fungal culture.
- Following organisms are diagnostic of infections. If identified, they are less likely to be the contaminants/colonizers and should be treated: Pneumocystis carinii, *Toxoplasma gondi*i, Strongyloides stercoralis, *Legionella pneumophila*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Mycobacterium tuberculosis*, *Mycoplasma pneumoniaee*, Influenza a and b viruses, Respiratory syncytial virus. (2A)
- Open/Video-assisted thoracoscopy (VATS)/CT guided/ transbronchial biopsy should be done in patients with lung infiltrates where the non-invasive testing/BAL haven't been able to provide the diagnosis and who have failed to respond to therapy, after risk-benefit assessment on case to case basis (2A).
- Any prior microbial colonization or antimicrobial resistance pattern of particular organisms should be considered while deciding empiric treatment for *pneumoniae* in SOT patients, particularly so in case of colonization of airway in lung transplant patients (3A).
- Empiric antibiotic therapy with carbapenem based on local susceptibility patterns for suspected community-acquired bacterial *pneumoniae* along with coverage of atypical/ intracellular pathogens like *Mycoplasma pneumoniaee*, *Chlamydia pneumoniae*, and *Legionella* spp. is recommended (2A). For the coverage of latter, among macrolides, consider using azithromycin instead of clarithromycin or erythromycin because of its relatively less likelihood to interact with immunosuppressants.
- For suspected viral *pneumoniae*, adding antiviral for influenza should be considered (2A).
- We recommend empiric treatment of recipients requiring hospitalization for *pneumoniae* with broad-spectrum antibiotics (carbapenem ± antipseudomonal ± anti MRSA) depending on local flora and resistance patterns, along with coverage for atypical organisms (2A).

- Antipseudomonal agent/polymyxin should be added if the patient is admitted in the hospital for ≥48 hours before symptoms (nosocomial *pneumoniae*) (2A), visited medical care (hemodialysis, wound care, immunosuppressants) within the previous 30 days, or hospitalized in an acute care hospital ≥2 days within the prior 90 days (UPP).
- Empiric antifungal therapy may be initiated where there is strong suspicion based on the clinical and radiological profile of the patient (3B).
- Empiric therapy should be initiated/modified as per clinical, radiological and microbiological findings and response (2A).

CMV Management

It has been recommended to use the standardized definitions of CMV infection and disease in transplant patients.[778,779]

CMV Infection

presence of CMV replication in tissue, blood, or other bodily fluids regardless of symptomatology detected by (a) nucleic acid testing (NAT), (b) antigen testing, and (c) viral culture.[780]

Asymptomatic CMV Infection

CMV replication without clinical signs and symptoms of disease.[781]

CMV Disease

CMV infection that is accompanied by clinical signs and symptoms. (a) CMV syndrome, (b) end-organ CMV disease. CMV has a predilection to invade the transplanted allograft; hence, CMV more commonly causes hepatitis in liver recipients, nephritis in kidney recipients, or pneumonitis in lung recipients.

Refractory CMV Infection

CMV DNAemia or antigenemia increases (i.e., >1 log10 increase in CMV DNA levels in blood between peak viral load within the first week and the peak viral load at 2 wk or more) after at least 2 wk of appropriately dosed antiviral therapy.

Refractory CMV Disease

Worsening in signs and symptoms or progression into end-organ disease after at least 2 wk of appropriately dosed antiviral therapy. Resistant CMV—Presence of viral genetic alteration that confer reduced susceptibility to one or more antiviral drugs.[781]

It is strongly recommended that CMV-IgG serology be done for all organ donors and transplant recipients in the preoperative period to evaluate their baseline immune status and both be interpreted together to assess the risk of posttransplant CMV risk in the recipient and thus guide the prophylaxis accordingly.[778] Recipients who are CMV seronegative (R–) and receive organ from a seropositive donor (D+), (that is D+/R–) have the maximum risk of developing CMV disease in the post-transplant period.[782,783] Severe lymphopenia (decreased number of lymphocytes) or lymphocyte anergy (decreased function of lymphocytes) due to drug induced immunosuppression is associated with higher risk of CMV after SOT.[800,801]

CMV IgM and IgG serology should not be used for the diagnosis of CMV disease after SOT as these patients might not mount a robust antibody response. The detection of CMV in the post-transplant period may be done by molecular assays (CMV QNAT-quantitative nucleic acid amplification test), pp65 antigenemia, histopathology and viral culture, CMV DNA by QNAT being the preferred one.[778] A positive correlation between higher viral load and end organ disease has been observed.[786,787] Detection of CMV by QNAT in BAL fluid and cerebrospinal fluid (CSF) can also be done. High viral load in BAL fluid has been found to be associated with CMV *pneumoniae*, however there isn't any standard threshold to define the same.[788] Positive CMV QNAT in CSF might be indicative of possible CNS CMV disease.[796] For end organ CMV disease, histopathologic diagnosis remains the gold standard modality, except for CMV retinitis, which is diagnosed based on ophthalmologic examination.[778,780] In a retrospective study, the response to therapy was assessed using RT-PCR (2262 samples) and antigenemia using pp65 assay (1285 specimens). Both methods had >90% specificity, but RT-PCR had better sensitivity. The authors concluded that RT-PCR was a more reliable tool to monitor the response to therapy.[789]

For the prevention of CMV disease in SOT recipients, either the antiviral prophylaxis or the pre-emptive therapy may be used, but in lung transplant recipients where only the prophylaxis is recommended. Valganciclovir and intravenous ganciclovir are the antivirals recommended for CMV prophylaxis and CMV disease.[788,790] Oral ganciclovir should not be used due to poor bioavailability. Limaye et al. compared letermovir (a novel viral terminase inhibitor) versus valganciclovir for prophylaxis in high risk kidney transplant recipients (D+/R–) in a randomized control trial and found it to be noninferior to valganciclovir.[791] Asberg et al. in a randomized controlled trial compared the outcome of CMV disease after treatment with IV Ganciclovir and oral valganciclovir. Three hundred twenty-one SOT recipients were enrolled and randomized to receive either twice daily intravenous ganciclovir or oral valganciclovir for 21 days followed by once daily valganciclovir until day 49 in all the patients. All patients were followed up for 1 year. The success rate was the same in both the groups with a similar rate of clinical and viral eradication. The clinical recurrence rate was also not statistically different in both the groups.[792] Valacyclovir in high doses may be used for prophylaxis only in renal transplant patients as an alternative.[793] The duration of antiviral prophylaxis has been summarized in Table 5.[778]

Due to the prescription of antiviral prophylaxis initially after transplant, CMV disease tends to occur in CMV D+/R– SOT recipients during 3–6 months after completion of antiviral prophylaxis and is termed as "post-prophylaxis delayed-onset CMV disease" compared from truly late-onset CMV diseases that occur many years after transplantation.[778] Pre-emptive therapy with oral valganciclovir (900 mg twice daily) or intravenous ganciclovir (5 mg/kg twice daily), which is another way of prevention of CMV disease, is initiated when the viral load reaches the predefined threshold and continued until virologic clearance (undetectable or level below predefined threshold).[794,795] Various studies have demonstrated the efficacy of intravenous ganciclovir for treatment of CMV disease and also shown comparable efficacy of valganciclovi and intravenous ganciclovir and have suggested that duration of therapy should be individualised as per the clinical response and the viral clearance.[792,796,797] There is a direct association between viral suppression below the lower limit of quantified test and disease resolution. Rapid resolution of CMV disease is seen with lower pre-treatment viral load (lower than 18,200 IU/mL).[798] The dose of antivirals should not be reduced for neutropenia.[755] For patients with suspected resistant CMV disease, high dose ganciclovir (10 mg/kg every 12 hours, renally adjusted) or foscarnet as empiric therapy can be initiated, pending the results of genotype testing according to which the therapy should be modified. In patients with resistant

Table 5: Recommendations for antiviral prophylaxis in SOT recipients

	Duration of antiviral prophylaxis					
Organ transplanted	*Heart*	*Lung*	*Kidney*	*Liver*	*Pancreas*	*Intestinal*
CMV serostatus						
CMV D+/R–	3–6 months	6–12 months	6 months	3–6 months	3–6 months	6 months
CMV R+	3 months	6–12 months	3 months	3 months	3 months	3 months
CMV D-/R–	Not recommended					

CMV, cytomegalovirus; D+, D, donor seropositive and seronegative respectively; R+, R–, recipient seropositive and seronegative respectively

or refractory disease, cautious reduction in immunosuppression is recommended and immunoglobulins may be used as adjunct to antiviral therapy.[778]

Evidence Statement

CMV reactivation risk is increased in post SOT patients due to immunosuppression induced lymphopenia and lymphocyte anergy. Preoperative CMV-IgG serology of donor and recipient can be used to assess risk and guide prophylaxis. In posttransplant period, CMV DNA using quantitative nucleic acid amplification is the diagnostic modality of choice. Detection of CMV by QNAT in BAL fluid and cerebrospinal fluid (CSF) is feasible. For end organ CMV disease, histopathologic diagnosis is the gold standard. CMV retinitis is diagnosed based on ophthalmologic examination. RT-PCR was a more reliable tool to monitor the response to therapy. Pre-emptive therapy is used for most SOT recipients, however, lung transplant patients should receive prophylaxis. Valganciclovir and intravenous ganciclovir have good efficacy and are used for prophylaxis and disease respectively. Letermovir has been shown to be noninferior to valganciclovir for prophylaxis in post renal transplant patients. Post prophylaxis delayed onset CMV disease occurs in donor positive recipient negative SOT recipients three to six months after completion of antiviral prophylaxis and should be treated with pre-emptive therapy. High dose ganciclovir or foscarnet are effective in empiric reatment of refractory disease, along with cautious reduction in immunosuppression. Immunoglobulins as adjunct therapy have been used in refractory disease.

Recommendation

Antiviral Prophylaxis

- Antiviral prophylaxis should be initiated within 10 days post SOT in all at-risk recipients for prevention of CMV infection/disease (1A).
- Valganciclovir (oral 900 mg once daily) or intravenous ganciclovir (5 mg/kg IV once daily) should be used for prophylaxis in all SOT recipients. Only in Post-kidney transplant patients, high dose oral valacyclovir (2 Gram qid) may be used as an alternative agent (1A).
- The duration of prophylactic therapy depends upon the CMV serostatus of the donor (D) and recipient (R) pre-transplant and the specific organ transplanted (Table 5).
- For patients receiving lymphocyte-depleting anti-lymphocyte antibodies (e.g., anti-thymocyte globulin ATG) for rejection, antiviral prophylaxis with valganciclovir or intravenous ganciclovir should be initiated (1A).

Pre-emptive Therapy

- Pre-emptive therapy for prevention of CMV disease in asymptomatic CMV infection in SOT patients (tested weekly post-transplant for up to 12 weeks or longer) with valganciclovir 900mg twice daily or intravenous ganciclovir (5 mg/kg twice daily) should be initiated once the predefined viral load threshold has been achieved, and duration be guided by viral load monitoring (i.e., CMV DNAemia or antigenemia below the predefined threshold or not detected) (1A).
- Antiviral prophylaxis is preferred over pre-emptive therapy for prevention of CMV disease heart transplant patients (1A).
- Preemptive therapy is not recommended for prevention of CMV disease in lung transplant patients (1A).

Therapy for CMV Disease

- We recommend CMV DNA by QNAT as the laboratory method of choice for rapid diagnosis of CMV infection in blood after SOT (1A).
- We recommend treatment of CMV disease with intravenous ganciclovir (5 mg/kg 12th hourly) or oral valganciclovir (900 mg twice daily) (in renally adjusted dosages) (1A).
- For severe or life-threatening CMV disease, very high viral load, and doubtful gastrointestinal absorption, use of intravenous ganciclovir is recommended (1A).
- Oral valganciclovir is an effective initial therapy for mild to moderate CMV disease (I, A), or as a step down to intravenous ganciclovir after clinical improvement (2B).
- Foscarnet and cidofovir can be used only as second-line agents for SOT recipients (due to high risk of nephrotoxicity associated) who are unable to tolerate intravenous ganciclovir or valganciclovir (2A).
- We recommend against use of acyclovir, valacyclovir, and oral ganciclovir for treatment of CMV disease (1A).
- We recommend a duration of treatment with antiviral for a minimum of two weeks and till there is resolution of clinical signs along with viral clearance as tested by weekly CMV quantitative NAT (QNAT: polymerase chain reaction- PCR) (1A).
- After completion of full-dose antiviral treatment, a 1 to 3 months course of secondary prophylaxis may be considered depending on the clinical situation (2B).
- We recommend monitoring complete blood count with differential and serum creatinine weekly for assessment of potential hematologic and renal toxicity (1A).
- The drug dosage of antiviral should be adjusted as per the renal function test (1A).
- The drug dosage of antiviral should not be decreased due to neutropenia or pancytopenia (1A). Hemopoietic growth factors may be used to counter the myelosuppressive effect of the drugs.
- Cautious reduction in immunosuppression should be considered in SOT patients presenting with CMV disease, especially if the disease is moderate to severe, or with severe lymphopenia or with refractory/ resistant CMV disease (2B).

Table 6: Causes of diarrhea in solid organ transplant recipients

Infectious			*Non-infectious*	
Bacterial	*Viral*	*Parasitic*	*Immunosuppressant drugs*	*Other drugs and etiologies*
Clostridium difficile	Cytomegalovirus	Giardia	Mycophenolate (most common)	Antibiotics, oral hypoglycemic agents
Small bowel bacterial growth (SBBO): *Escherichia coli*, Campylobacter, Shigella, Salmonella	Norovirus	*Cryptosporidium*	Tacrolimus	Proton pump inhibitors, laxatives
	Adenovirus	Entamoeba	Cyclosporine	GVHD, PTLD
	Rotavirus, Sapovirus, Enterovirus, Human herpes virus 6	Isospora belli Microsporidium	Sirolimus	Colon cancer Inflammatory bowel disease

GVHD, graft versus host disease; PTLD, Post-transplant lympho-proliferative disorder

- Empiric treatment of suspected resistant CMV disease include high-dose intravenous ganciclovir (up to 10 mg/kg q12 hours, renally adjusted) or foscarnet. Definitive antiviral treatment should be guided by results of genotypic testing (2B).
- CMV immunoglobulin or IVIg may be used as an adjunct to antiviral drugs in transplant recipients with life-threatening disease, CMV pneumonitis or resistant CMV disease (2B).

Tuberculosis (TB) in SOT Recipient

Given that tuberculosis is an immunological disease and with the high prevalence of TB in India, the incidence of active tuberculosis infection is higher among SOT recipients as compared to the general population. The diagnosis of TB in SOT recipients presents challenges that may lead to treatment delay. These include atypical clinical presentations, increased likelihood of negative tuberculin skin tests and/or IGRA, and negative sputum smear results despite active disease makes TB diagnosis in SOT recipients a challenge.[799–805] Radiological investigations like CT scan and the invasive modalities like BAL with or without biopsy should be performed early in case of suspicion of TB. One-third to one-half of cases of tuberculosis after transplant are disseminated or extrapulmonary. Lung transplant recipients are most likely to develop pulmonary manifestations of TB. Drug-drug interactions between immunosuppressive and AKT, allograft-related drug toxicities, and inadequate immune responses to TB makes treatment of TB in transplant recipients also very challenging.[801,805] The standard 4 drug regimen should be used wherever possible[803] and if necessary, rifampicin can be replaced by levofloxacin. In the latter case, 4 drugs, that is, isoniazid (INH), ethambutol, pyrazinamide and levofloxacin are given for 2 to 3 months for initiation and then 3 drugs (INH, ethambutol and either pyrazinamide or levofloxacin) continued to complete the therapy duration of 12 months.[805] Using rifamycin as one of the drugs for the treatment of post-transplant TB would increase the cost significantly because of the high doses of CNIs/mammalian target of rapamycin inhibitors needed to maintain the levels and the requirement for frequent drug monitoring. So, the South Asian Transplant Infectious Disease Guidelines for solid organ transplant *Candida*tes, recipients, and donors recommends a rifamycin-free regimen as the standard approach to treating posttransplant TB in this region except in special situations.[805]

Evidence Summary

Incidence of tuberculosis is higher as compared to general population. Up to 50% cases of tuberculosis can be disseminated or extrapulmonary in post SOT patients. Atypical clinical presentations, less sputum positivity and false negative tuberculin and IGRA tests lead to delays in diagnosis. Radiological investigations like CT scan along with bronchoscopy, BAL or histopathologic evaluation from involved site are needed for prompt diagnosis. Rifampin containing regimens reduce serum concentrations of tacrolimus, cyclosporine, sirolimus and everolimus, whereas rifampin free regimens increase the duration of antitubercular therapy.

Recommendation

- The diagnosis of active TB in transplant recipients requires a high index of suspicion. Although the diagnostic modalities and treatment of TB in SOT patients remains the same as that in immunocompetent hosts, these individuals often require an invasive procedure, such as bronchoscopy with BAL or lung biopsy (1A).
- Rifamycins, particularly rifampin, reduce serum concentrations of tacrolimus, cyclosporine, rapamycin (sirolimus), and everolimus via induction of the cytochrome p450 isoenzyme CYP3A4, necessary dose adjustments, and therapeutic drug monitoring are warranted to avoid development of rejection (II, A). When rifampin is not used, a longer than usual duration of treatment is required (2B).

Infective Diarrhea in SOT Recipient

Diarrhea of varied etiology is a common occurrence in post-transplant patients, incidence ranging between 17 to 50%. It can be attributed to infectious and non-infectious causes, which have been summarized in Table 6.[806] As per the DIDACT study from Belgium on etiology of diarrhea in renal transplant recipients, drug-induced diarrhea was most common (70%) followed by infectious etiology (bacterial infection 20% and CMV 7%).[807] In a study analysing the etiological profile of diarrhea in SOT recipients at a tertiary care center in Southern India, they found that of the 58 episodes of diarrhea in 55 recipients, 70% were reported in renal transplant recipients. 79%of the patients were >6 months post-transplant. Infective diarrhea was the etiology in 46%, drug-related diarrhea in 29.3% and no specific etiology was identified in 22.4% of patients. Of the cases with infective diarrhea, parasites were responsible for 69%. Stool analysis included wet mount examination for ova, trophozoites, and cysts, modified acid-fast staining for *Cryptosporidium* spp, *Isospora belli*, *Cyclospora cayetanensis,* and modified trichrome stain for *Microsporidia* spp., *C difficile* toxin assay using ELISA method for detection of glutamate dehydrogenase antigen and toxin A and B; stool culture in selected patients.[808] In another Indian study on etiological spectrum of infective diarrhea in renal transplant patients by stool PCR, they found that 86% of the stool samples were positive for infection and 68% had more than one organism identified. The most common pathogen isolated was Norovirus and *Giardia lamblia* with Norovirus was the most

common coinfection.[809] Due to frequent exposure to antibiotics and repeated hospitalizations SOT patients are a risk of developing intra-abdominal infections (IAI). It is recommended for all SOT patients with diarrhea to undergo stool testing for C. Difficile, CMV, and bacterial pathogens, also considering multiplex PCR testing, testing for parasites and Norovirus (stool PCR).[806] The medications that the patient is on should be reviewed and any possibly responsible ones should be withheld. Those not responding to therapy, or negative infectious screening or having chronic diarrhea should be evaluated using colonoscopy with or without biopsy. The initial management of *C difficile* infection (CDI) remains similar to non-transplant patients.[806] The American Society of Transplantation Infectious Diseases Community of Practice have recently published updated guidelines to address the prevention and management of CDI in SOT recipients.[810] Vancomycin 125 mg PO QID or fidaxomicin 200mg PO BID 10–14 days is the preferred treatment for initial mild to moderate CDI. FMT should be considered for second further recurrences. For fulminant disease, vancomycin PO 500 mg q.i.d. and vancomycin via rectal administration and metronidazole 500 mg intravenously Q6–Q8 h should be prescribed and surgical consultation should be sought.[810,811] A series of cases (75 adults and 5 pediatric patients) treated with FMT for recurrent, refractory, and severe and/or overlap of recurrent/refractory and severe CDI had 78% cure rate after first FMT. There were no related infectious complications or adverse events in these high-risk patients.[812]

Evidence Statement

Diarrhea in posttransplant patients can be due to infectious and non-infectious causes. Drug induced diarrhea and infections are most common reported causes. Bacterial infections, parasitic infections (giardiasis) and viral infections (CMV, norovirus) are common infectious causes. Due to frequent exposure to antibiotics and frequent hospitalization, *clostridium difficile*-associated diarrhea is also common. Stool investigations should be performed for all suspected organisms. The initial management of *C difficile* infection (CDI) remains similar to non-transplant patients.

Recommendation

- We recommend empiric management of gastrointestinal infections/ diarrhea with ceftriaxone IV + ganciclovir 5mg/kg BD IV and vancomycin 125mg PO QID (if the patient is already on antibiotics to cover CDI) till definitive diagnosis is made (1A).
- If the patient is in septic shock, based on local resistance pattern, and previous drug history of patient consider carbapenems (UPP).
- We recommend cessation of the inciting antimicrobial agent whenever possible (2A).
- We recommend using a NAAT alone or a multistep algorithm for testing (i.e., GDH plus toxin; or NAAT plus toxin) rather than a toxin test alone for the diagnosis in stool specimens likely to be having *Clostridium difficile* infection CDI (2A).
- For treatment of CDI in adults, either vancomycin (125 mg given 4 times daily orally for adults; 40 to 50 mg/kg/day divided QID for pediatric patients, not to exceed adult dosing; for 10–14 days) or fidaxomicin (200 mg given twice daily orally for 10 days) is recommended over metronidazole (1A). If these agents aren't available, metronidazole 500 mg 3 times daily by mouth can be used as an alternative.
- We recommend oral vancomycin up to 500 mg orally QID in adults for the treatment of severe/fulminant CDI (I, A). If ileus, consider adding rectal instillation of vancomycin 500 mg in 100 mL normal saline as retention enema 4 times a day (2B).
- Intravenous metronidazole 500 mg intravenously every 8 hours may be administered together with oral or rectal vancomycin (1B).
- In cases of multiple recurrences of CDI, we recommend prolonged courses of oral vancomycin, either in a tapering or pulse dose schedule (2A). Fidaxomicin can be used if available (2B).
- Fecal microbiota transplant (FMT) may be considered in recurrent or relapsing CDI (2B).
- We suggest consideration for surgical intervention in cases of complicated CDI (2B).

Invasive Fungal Infection in SOT Recipients

The epidemiology of fungal infections in posttransplant patients depends upon certain host and environmental factors.[813] The highest risk of first invasive fungal infection (IFI) among SOT recipients as reported by TRANSNET network (2010) has been found in small bowel transplant followed by lung, liver, heart, pancreas and kidney transplant in that order (the one year cumulative incidences being 11.6%, 8.6%, 4.7%, 4%, 3.4%, and 1.3%, respectively). Invasive candidiasis (IC) was the most common IFI (53%) followed by invasive aspergillosis (IA) (19%), cryptococcosis (8%), non *aspergillus* molds (8%), endemic fungi (5%) and zygomycosis (2%). Median time to onset of IC was 103 days, 184 days for IA and 575 days for cryptococcosis. They observed an increase in cumulative incidence of IFIs during the surveillance period.[814] Emerging *Candida* strains that are drug resistant are a cause for concern and pose challenge in the management. Indian data regarding epidemiology of IFI in SOT is scarce.[815] In a review by Sharma et al., the maximum available data was from renal transplant patients and they found mucormycosis to be the predominant. They reported an increase in IFIs and more renal transplant patients acquiring mucormycosis during the COVID-19 outbreak.[816]

As per a review, IC is the most common the IFI in India, followed by mucormycosis, IA, and cryptococcosis; and prevalence of azole and multidrug resistance among *Candida* infections in South Asia is increasing. They reported that the most common endemic mycoses in Asia-Pacific region are histoplasmosis, talaromycosis and sporotrichosis.[817] Another recent publication showed 67 (9.2%) of 725 renal transplant recipients had IFIs. Invasive candidiasis was the most common IFI followed by mucormycosis, IA, and cryptococcosis.[818] As per TRANSNET 2016 on *Candida* infections, among IFI in SOT patients IC constituted 50–60%. Most of them are bloodstream infections (44%), followed by intra-abdominal (14%), and they occurred mostly in liver (41%) and kidney (35%) transplant. Mortality is higher in liver transplant.[819] Blood cultures are the mainstay of diagnosis. Non-culture based methods such as 1,3 beta-D glucan or T2 *Candida* assay maybe used in patients suspected of having IC, if culture and/or histopathology of tissue are not available or negative.[820]

IA infections incidence was higher in lung and heart transplant recipients.[69] CT scan is able to give diagnosis of IPA in only half of the patients, direct examination of respiratory secretions in 49% and culture in 70%, BAL galctomannan in 39% and serum galactomannan (GM) in 35%.[821] Serum GM is not recommended for diagnosing IA. A retrospective study involving 362 lung transplant recipients found that 105/335 (31%) patients had evidence of *aspergillus* infection (colonization or invasion), 83 (25%) patients had

colonization and 22 (6%) patients had radiographic or histological evidence of invasive disease. Most of the infections occurred within the first 3 months after transplantation. Invasive aspergillosis (IA) was associated with 58% mortality after 2 years, while colonization was associated with increased mortality after 5 years compared non-colonised patients ($p < 0.05$).[822]

Voriconazole remains the drug of choice for treatment of IA, isavuconazole and lipid formulations AmpB being the alternative agents. Infectious Diseases Society of America (IDSA),[725] the European Society for Clinical Microbiology and Infectious Diseases[823] and American Society of Transplantation Infectious Diseases Community of Practice (AST-IDCOP)[821] endorse this recommendation. Echinocandins should be used alone or in combination only as salvage therapy.[725] Herbrecht et al.[824] compared voriconazole with amphotericin B in a large randomized trial for the treatment of IA in immunocompromised patients. In their study they found that at week 12, there were more successful outcomes 52.8% patients in the voriconazole group (complete response 20.8% and partial response in 31.9%) compared to 31.6% in the amphotericin B group (complete response 16.5% partial response in 15%). The survival rate was better at 12 weeks in voriconazole compared to amphotericin B group. (71 vs 58%) (HR –0.59; 95% CI, –0.40 to 0.88). Denning et al. in their study showed good response in IA treated with voriconazole; 56 out of 60 patients in voriconazole group were treated successfully.[825] Voriconazole was successfully used in heart transplant recipients as first-line and salvage therapy for IA.[826,827]

Isavuconazole was found to be non-inferior to voriconazole for the primary treatment of invasive mold disease caused by *Aspergillus* and other filamentous fungi, in a trial conducted in hematological patients (SECURE RCT). All cause mortality through day 42 was the primary endpoint and was found to be 19% and 20% in isavuconazole and voriconazole group respectively. The former has been found to be associated with lesser visual, skin/subcutaneous tissue, and hepatobiliary side-effects.[734]

Therapeutic drug monitoring (TDM) for azole antifungals (especially voriconazole and posaconazole) should be done and all current guidelines recommend the same.[725,821,823] Plasma drug level monitoring is important when voriconazole is used as the plasma levels achieved are variable and very often do not reach therapeutic levels in the plasma, requiring dose adjustments.[828] The fact that clinical efficacy is dependent on the achievement of therapeutic drug levels has been well established.[829]

For IC or candidemia, echinocandins remain the drug of choice and in a clinically stable patient it can be switched to fluconazole if the *Candida* isolate is susceptible to fluconazole. Antifungal should be continued for minimum 2 weeks after first negative fungal blood culture and till the resolution of features of IC.[725,820] Antifungal prophylaxis for IFI depending upon the host factors and the organ transplanted has been recommended.[817,820,821]

Evidence Statement

SOT recipients are at increased risk of fungal infections, highest risk in small bowel transplant, followed by lung, liver, heart, pancreas and kidney transplant. Invasive candidiasis is most common fungal infection, followed by aspergillosis, cryptococcosis, non-*aspergillus* molds, endemic fungi and zygomycosis. Emerging *Candida* strains that are drug resistant are a cause for concern and pose challenge in the management. India data is limited, and mucormycosis is the commonest infection. *Candida* infections are most commonly bloodstream infections followed by intraabdominal infections. *Aspergillus* colonization and infection is associated with increased mortality in lung transplant recipients. Various diagnostic modalities including serum markers such as beta-D glucan, galactomannan, imaging (CT scan), bronchoscopic evaluation or histologic evaluation of involved site lead to early diagnosis.

Voriconazole remains the drug of choice for treatment of IA, isavuconazole and lipid formulations AmpB being the alternative agents. Echinocandins can be used as salvage therapy. Isavuconazole is non-inferior to voriconazole for the primary treatment of invasive mold disease caused by *Aspergillus* and other filamentous fungi. Therapeutic drug monitoring (TDM) for azole antifungals (especially voriconazole and posaconazole) improves clinical efficacy and is preferred. For IC or candidemia, echinocandins remain the drug of choice and in a clinically stable patient it can be switched to fluconazole if the *Candida* isolate is susceptible to fluconazole. Duration is dependent on culture negativity and resolution of features of invasive candidiasis.

Recommendation

Antifungal Prophylaxis

Recommendations for antifungal prophylaxis in different solid organ transplant recipients are enumerated in Table 7 and Table 8.

Invasive Aspergillosis (IA) Treatment

- It is recommended not to use serum galactomannan (GM) to diagnose IA in SOT patients (1A)
- Serum or BAL beta-D-Glucan should not be used to screen or diagnose SOT patients for IA (1B).
- BAL GM is the preferred parameter for diagnosis of invasive pulmonary aspergillosis and a value of ≥1.0 in combination with other fungal diagnostic methods is used to diagnose IA in SOT recipients (1A).
- For IA or positive BAL galactomannan, we recommend voriconazole in the dose of 6mg/kg bd for 1 day f/b 3mg/kg bd (1A).
- Isavuconazole and lipid formulations of Amphotericin B (AmB) can be used as alternative agents (1A).
- As a salvage therapy, posaconazole can be used where patients fail to respond or are intolerant to first line agents (1B).
- Echinocandins are not recommended as a primary therapy (1B) and can be used only as a salvage therapy or as a second agent where combination therapy is being considered (3B).
- We recommend therapeutic drug level monitoring (TDM) for voriconazole when using it for the treatment of IA (1A).
- We recommend that treatment be continued for minimum 12 weeks, if tolerated, and guided by clinical and radiological response (1A).

Other Emerging Fungal Infections

- For infection by mucormycetes, lipid formulations of AmB is the drug of choice for induction therapy (1A).
- Posaconazole or isavuconazole can be used as alternative agents for induction and for maintenance therapy (2B).
- Surgical excision or debridement is recommended for all wherever feasible, particularly for mucormycetes infection outside of lungs (2A).
- For trichosporon, azoles are the recommended first line agents (3A), subject to the susceptibility.

Table 7: Anti fungal prophylaxis (for *Candida*) in Solid organ transplant recipients

		Candida		
Organ transplanted	*Universal prophylaxis*	*Targeted prophylaxis*	*Drug*	*Duration*
Liver	May be given (UPP)	Should be given in patients at high risk of invasive candidiasis (1A) e.g.: • Re-transplantation • Renal replacement therapy at the time of or within 7 days of transplantation. • Choledochojejunostomy. • Perioperative *Candida* colonization • Transfusion of ≥40 units of cellular blood products. • MELD score ≥30 • Fulminant hepatic failure • Biliary leak	• Azoles or echinocandins preferred over amphotericin B lipid formulation (1A). • Fluconazole is the drug of choice (1B).	2 to 4 weeks (2B)
Small bowel	Recommended (1B)	In high risk patients: graft rejection or dysfunction, enhanced immunosuppression, anastomotic disruption, abdominal reoperation, or multivisceral transplantation	Fluconazole Others if higher prevalence of *Candida* non albicans or prior azole exposure	4 weeks or until the anastomosis has healed, and no rejection (1A, 1B)
Pancreas	Not recommended	When at least one risk factor associated with candidiasis is present: (2B) Enteric drainage, Vascular thrombosis Post-perfusion pancreatitis	Fluconazole (Others if higher prevalence of *Candida* non albicans)	Depend on reduction in risk factors
Heart	Not recommended (1B)			
Kidney	Not recommended (1B)			

Table 8: Anti fungal prophylaxis (for *Aspergillus*) in Solid organ transplant recipients

		Aspergillus		
Organ transplanted	*Universal prophylaxis*	*Targeted prophylaxis*	*Drug*	*Duration*
Liver	Not recommended (1A)	In high risk cases: Re-transplantation Renal replacement therapy Reoperation involving thoracic or intra-abdominal cavity	Echinocandin or voriconazole (1A). Lipid formulation of amphotericin B 3-5 mg/kg may be considered (2B)	14 to 21 days (1A)
Lung	Recommended (1A)	Recommended in: • Pre-transplant *Aspergillus* colonization • Post-transplant *Aspergillus* colonization within a year of transplant • Single-lung transplant • Positive intraoperative *Aspergillus* culture in patient with cystic fibrosis	Systemic antifungal for prophylaxis or preemptive therapy : Voriconazole (6 mg/kg for two doses followed by 4 mg/kg every 12 h), itraconazole or posaconazole. Nebulized L-AmB or ABLC for prophylaxis (II,B)	4 to 6 months (1A)
Heart	Not recommended	• Recommended in : Isolation of *Aspergillus* species in respiratory tract cultures without radiological abnormality. • Presence of airborne *Aspergillus* spores in the ICU • Re-operation(thoracic) Presence of CMV disease • Post-transplant hemodialysis	Itraconazole or voriconazole OR Echinocandins (1B)	Up to 150 days
Other SOTs	No recommendation			

Pneumocystis Jirovecii Infection Management

The incidence of PCP in SOT recipients is variable. In a retrospective study of 1192 renal transplant patients, it was reported to be 0.6 to 9%. Authors observed that the incidence of PCP with a moderate cyclosporine based immunosuppressive regimen is low and seems to occur only in cases of additional immunosuppressive cofactors.[830] In another retrospective study of 601 renal transplant recipients, PCP incidence was 2.2%.[831] In liver transplant recipients (154 adult patients) PCP occurred in 5.2% and the authors observed that patients who developed PCP had more episodes of rejection ($p < 0.05$), received more OKT3 ($p < 0.05$), a prednisone ($p < 0.05$) than controls.[832] Another retrospective study of 43 adult OLT recipients showed that the incidence of PCP was 0.9%. Most of the patients developed PCP at around 1 year of post-OLT, and the risk of PCP was closely related to strong immunosuppressive regimen. Thus they advised that routine PCP prophylaxis for 12 months be continued for 12 months, among patients receiving antirejection treatment.[833]

TMP-SMX acts by interfering with folate metabolism and remains the drug of choice for treatment of PCP in SOT patients, HIV patients, and non-HIV patients. TMP-SMX has high efficacy and availability in both oral and IV preparation with good oral bioavailability too.[834] Intravenous pentamidine has been found to be equally effective in HIV-infected patients and remains the second line of choice for treatment of PCP in SOT patients.[835–839] However, the use of pentamidine has been largely limited in view of its numerous toxicities in 71% patients leading to withdrawal in around 18% patients.[836] The optimal duration of therapy is usually 14 days which can be extended to 21 days in severe cases with slow clinical improvement.[840] Adjunctive glucocorticoids are recommended for HIV- positive patients with moderate to severe PCP, defined as PaO_2 <70 mmHg while breathing ambient room air.[841] The benefit in survival from corticosteroids begins during the first 72 hours of treatment.[842]

With the provision of PJP prophylaxis, the incidence of PJP is less in the initial 6to 12 months posttransplant. However, in the absence of prophylaxis, risk of PJP is maximum in the first 6 months after SOT. TMP-SMX is the drug of choice for prophylaxis as well as treatment PJP.[843]

Evidence Statement

Incidence of PJP infections in SOT recipients ranges from 0.6% to 9% in various studies. Risk depends on degree of immunosuppression. PJP infection, in turn, leads to more episodes of rejection and increased need for steroids and immunosuppression. TMP-SMX has high efficacy and availability in both oral and IV preparation with good oral bioavailability. The optimal duration of therapy is usually 14 days which can be extended to 21 days in severe cases with slow clinical improvement. Adjunctive glucocorticoids are recommended for moderate to severe PCP. PJP prophylaxis reduces incidence of PJP in the first year after transplant.

Recommendation

Anti-pneumocystis Prophylaxis

- We recommend anti-pneumocystis prophylaxis to all SOT recipients for 6 to 12 months posttransplant, particularly for centers with incidence ≥3–5% among transplant recipients (1A).
- Longer duration of prophylaxis may be considered in patients with prior history of PJP (*Pneumocystis jirovecii pneumoniae*) infection, chronic CMV infection, higher intensity of immunosuppression, lung and small bowel transplant recipients, prolonged neutropenia (1A).
- Trimethoprim-sulfamethoxazole (TMP-SMX) is the drug of choice for prophylaxis of PJP, in a (adult) dose of either 80 mg TMP/400 mg SMX (single strength) daily or 160 mg TMP/800 mg SMX (double strength) orally three times weekly (1A).

PJP treatment

- We recommend TMP-SMX as the first-line agent and drug of choice with the Trimethoprim component being 15–20 mg/kg/day in 3 to 4 divided doses (1A).
- In severe infections, if available, intravenous pentamidine probably remains the second-line agent after TMP-SMX (2A). Its usage should be avoided in pancreas transplant recipients (1B).
- Primaquine and clindamycin in combination may be used as alternative in mild to moderate infection. However, primaquine should be avoided in G6PD deficient patients, and association of *clostridium difficile*-associated diarrhea (CDAD) with long term usage of clindamycin should be considered (2B).
- In patients with hypoxemia (PaO_2 <70 mmHg on room air), adjunctive corticosteroids should be administered with antimicrobial therapy, ideally within 72 hours of initiating antimicrobial therapy for maximum benefit (2A). The dose of steroids should be 1 mg/kg/day prednisone (or equivalent) given in two divided doses daily for 5 to 7 days (2A). Steroids should be tapered over a period of 7 to 14 days (2B).
- Duration of antimicrobial therapy should be for at least 14 days (1B).

CNS infections in SOT recipients

SOT patients with altered sensorium should be evaluated with detailed workup. Multifactorial etiologies coexist which are often obscured in these group of patients.[844] Although each imaging modality has unique insight to diagnose pathophysiology, but magnetic resonance imaging (MRI) is the preferred modality. It can diagnose infectious as well as non-infectious etiologies like drug toxicities, metabolic disorders as well as the progression of the disease and response to the therapy.[845,846] Empiric broad-spectrum antimicrobial therapy including viral and fungal infections are preferred. It is preferred to use empirical bactericidal or fungicidal agents having CNS penetration until a diagnosis is achieved.[844] There has been always a risk of donor-derived infections in SOT recipients thus donors should be screened with standard screening tests.[847,848]

Common pathogens causing CNS infections in SOT recipients are mentioned in Table 9.[757,849,850] In a Swiss Transplant Cohort Study (STCS), the incidence rate of CNS infection was 2.06 per 1000 patient-years and was similar across all types of transplantations. Time to CNS infection onset ranged from 0.6 to 97 months after transplant. Of the 4762 patients, 42 episodes of CNS infections were observed and 22/42 (52.4%) cases were viral infections, 11/42 (26.2%) fungal, 5/42 (11.9%) bacterial and 4/42 (9.5%) were of probable viral/bacterial etiology. Viral meningoencephalitis was the most common disease, and fungal infections were associated with a high mortality.[850]

Lipid amphotericin B plus 5-flucytosine is used as initial treatment of meningitis, disseminated infection, and moderate-to-severe pulmonary infection, followed by fluconazole as consolidation therapy.[851] Cryptococcosis is a significant opportunistic infection in SOT recipients following aspergillosis and candidiasis. CSF analysis is highly recommended to diagnose underlying CNS disease in

Table 9: Common organisms causing central nervous system infection in solid organ transplant recipients

Intracerebral abscess	*Meningoencephalitis*
• Bacterial: Embolic or contiguous disease from the local site • *Nocardia* • *Listeria monocytogenes* • Fungal: *Aspergillus*; Zygomycetes; *Cryptococcus* • EBV associated post-transplant lymphoproliferative disorder (PTLD) • *Mycobacterium tuberculosis* • Toxoplasmosis	• Bacterial: *S. pneumoniae*e, *Neisseri*a meningitides, *Listeria*, Gram-negative bacilli • Viral: CMV, EBV, HSV, VZV, HHV, Enterovirus, JC virus • Fungal: *Cryptococcus*, Coccidioides, *Histoplasma capsulatum* • *Mycobacterium tuberculosis* • Treponema pallidum • Borrelia burgdorferi

suspected cases.[852] *Cryptococcus* can colonize the airways of lung transplant recipients and can cause endobronchial fungal infection. It can present with skin manifestations and Immune reconstitution syndrome (IRIS) as well.[853,854]

They main components in management of cryptococcosis in SOT recipients include (a) performing lumbar puncture (for diagnostic purpose and for therapeutic purpose, that is, manage meant of intracranial pressure, which is often high in cryptococcal meningitis); (b) antifungal therapy (as described above); and (c) a gradual immunosuppression reduction (a rapid reduction can lead to development of IRIS).[851]

Evidence Statement

SOT patients with altered sensorium have multifactorial causes and need extensive work up, with MRI being the initial preferred imaging modality. Empirical regimens with bactericidal or fungicidal agents having CNS penetration are initiated at admission, until definitive diagnosis. Common pathogens causing CNS infections in SOT are viral followed by fungal and bacterial agents. Viral meningoencephalitis is most common CNS disease in large prospective studies. Thus, antibiotics covering both gram-positive and gram-negative pathogens along with Acyclovir is part of initial empiric regimen. Amphotericin B plus 5-flucytosine is used as initial treatment of cryptococcal meningitis.

Recommendation

- We recommend initial workup for suspected CNS infections should include (1A).
  - MRI over CT scan.
  - CSF analysis including India ink preparation.
  - Rapid multiplex PCR on CSF.
  - Serum cryptococcal antigen.
- We recommend empiric treatment to be started with Ceftriaxone + Vancomycin + Acyclovir (1A).
- We recommend liposomal Amphotericin B or AmB lipid complex (ABLC) plus flucytosine as the initial treatment for *Cryptococcus* for minimum 2 weeks for CNS disease, disseminated disease, or moderate-to-severe pulmonary disease (1A). Alternatively, liposomal AmB or ABLC can be used for minimum duration of 4 to 6 weeks (1B).

Nocardia in SOT Recipients

SOT recipients are at risk of developing *nocardia* infection which is an opportunistic event.[855,856] The risk of developing nocardiosis after SOT varies with the type of organ transplanted, e.g., the highest incidence in recipients of a lung transplant. A review of 5126 organ transplant recipients has demonstrated that highest *nocardia*l infection rate among lung transplant recipients (3.5%).[855,857] TMP-SMX is the treatment of choice for *nocardia*l infections as it has demonstrated clinical efficacy and achieves high tissue concentrations in lung, brain, skin, and bone. Combination therapy is recommended in critically ill patients with pulmonary *nocardia*, cerebral *nocardia*, and disseminated *nocardia*.[858] Linezolid has shown good activity against all species of *nocardia*.[859]

Evidence Statement

Nocardia infection can occur post solid organ transplants. Lung transplant patients seem to be at highest risk. TMP-SMX, carbapenems and linezolid have efficacy against *Nocardia*. Combination therapy is recommended in critically ill patients with pulmonary, cerebral and disseminated *nocardia*l infection.

Recommendation

We recommend the following regimens for treatment of post-transplant *nocardia* infections

1. Pulmonary: TMP-SMX (1A) (TMP-SMX 15 mg/kg in 3-4 divided doses, for 6 to 12 months)
2. Disseminated or CNS, Critically Ill: Imipenem plus TMP-SMX or Amikacin (2A)
3. Alternative: Linezolid, Meropenem (1A)

Multidrug-resistant (MDR) Infections in SOT Recipients

MDR gram-negative bacteria (GNB) infections- these recommendations have been adapted from AST-IDCOP[860] guidelines and the more recently published IDSA guidelines[861] for MDR-GNB infections.

For ESBL-producing *Enterobacter*iaceae, carbapenems are the drug of choice. For Carbapenem-resistant *Enterobacter*iaceae (CRE), ceftazidime/avibactam is preferred, and ceftazidime/avibactam plus aztreonam or cefiderocol as monotherapy for metallo-β-lactamase producing CRE is recommended for systemic infections. Tigecycline may be used as an alternative agent in non-urinary tract infections. For infections due to MDR *Pseudomonas aeruginosa*, high-dose continuous or extended-infusion antipseudomonal β-lactam or Ceftolozane/tazobactam or Ceftazidime/avibactam is recommended. For treatment of Carbapenem-resistant *Acinetobacter* baumannii infections, combination therapy with at least two agents, at least until clinical improvement is seen. High-dose ampicillin-sulbactam (total daily dose of 6-9 grams of the sulbactam component) is suggested as a component of combination therapy for CRAB, regardless of whether susceptibility has been demonstrated. Possible options to combine with it include: tetracycline derivatives (minocycline/ tigecycline), polymyxin B, or cefiderocol.

For management of MDR *Stenotrophomonas maltophilia*, either of the 2 approaches is recommended: 1) the use of two of the

following agents: TMP- SMX, minocycline/tigecycline, cefiderocol, or levofloxacin. 2) ceftazidime-avibactam plus aztreonam (when critical illness is evident or intolerance or inactivity of other agents is observed). Nadales et al. in their narrative review also focused on the contribution provided by INCREMENT-SOT project which is a large international retrospective cohort that includes nearly 800 consecutive SOT recipients diagnosed with bloodstream infection (BSI) due to ESBL-E and CRE between 2004 and 2016.[862]

For methicillin resistant *Staphylococcus aureus* (MRSA) bacteremia and *pneumoniae*, vancomycin remains the preferred initial drug of choice and the dose should be adjusted as per the serum trough levels or AUC/MIC ratio. For bacteremia, infective endocarditis, *pneumoniae*, and osteomyelitis target trough should be between 15 and 20 μg/mL or AUC/MIC >400. Teicoplanin has been found be as effective as vancomycin. Daptomycin can be used as an alternative agent where there is vancomycin intolerance or persistent bacteremia. It shouldn't be used for *pneumoniae* as it is degraded by surfactant. Linezolid may be used for skin and soft tissue infection (SSTI) and nosocomial *pneumoniae*. Ceftaroline, a fifth generation cephalosporin, has been approved for SSTIs, *pneumoniae* (community-acquired, nosocomial), but not particularly due to MRSA and is not approved for bacteremia. A lipoglycopeptide, dalbavancin has bactericidal activity against MRSA but is currently not approved for treatment of MRSA bacteremia.[863]

Evidence Statement

Carbapenems are effective for treatment of ESBL-producing *Enterobacter*iaceae. For Carbapenem-resistant *Enterobacter*iaceae (CRE), preferred antibiotics are ceftazidime/avibactam is preferred, whereas and ceftazidime/avibactam plus aztreonam or cefiderocol monotherapy are useful in metallo-β-lactamase producing CRE. Tigecycline is useful in treatment of CRE infections outside the urinary tract, and in absence of bacteremia, as combination therapy. For MDR *pseudomonas*, effective drugs are antipseudomonal β-lactam or Ceftolozane/tazobactam or Ceftazidime/avibactam. For carbapenem resistant acinetobcacter, high dose ampicillin-sulbactam, tetracycline derivatives (minocycline/tigecycline), polymyxin B, or cefiderocol are options for combination therapy. For MDR *Stenotrophomonas maltophilia*, combination therapy with two agents (TMP- SMX, minocycline/ tigecycline, cefiderocol, or levofloxacin) is effective. However, critically ill patients can be treated with ceftazidime-avibactam plus aztreonam. For MRSA, vancomycin with therapeutic drug monitoring has most evidence. Linezolid can be used for skin and soft tissue infection (SSTI) and nosocomial *pneumoniae*. Teicoplanin is another efficacious alternative.

Recommendation

Empiric antibiotics for MDR pathogens should be chosen to cover the suspected pathogen spectrum and local microbiology (2A)

The Human Immunodeficiency Virus (HIV) Positive Patient in the Intensive Care Unit

AIDS in adults is defined by Polymerase chain reaction (PCR)-confirmed HIV-positivity plus World Health Organization (WHO) stage IV disease (i.e., esophageal or bronchial candidiasis, wasting syndrome, central nervous system toxoplasmosis, *Pneumocystis jirovecii pneumoniae* (PCP), recurrent severe bacterial *pneumoniae*, chronic herpes simplex infection, Kaposi's sarcoma, Cytomegalovirus (CMV) infection, chronic cryptosporidiosis or isosporiasis, extrapulmonary cryptococcosis, disseminated endemic mycosis [coccidiomycosis or histoplasmosis] or non-tuberculous *mycobacteria*l infection, extrapulmonary tuberculosis (TB), HIV encephalopathy, cerebral B-Non-Hodgkin-Lymphoma, progressive multifocal leukoencephalopathy (PML), symptomatic HIV-associated nephropathy, or cardiomyopathy) or immunological diagnosis with HIV-infection or first documented CD4+ cell count <200/μL.[864] Since the first case report of HIV in 1981, we have come a long way. The HIV infected patients now have a normal life expectancy when treated with combination ART (cART). Successful HIV treatment can result in full suppression of the virus. cART is now started within 2 weeks of diagnosis as opposed to previous practice of delaying till the CD4 counts fell. Low CD4 cell counts predisposes patients to certain infections but in critical illness, the circulating CD4 count may be even lower as they are redistributed to the activated tissue.[865–869]

There is an increased risk of chronic conditions in HIV patients such as atherosclerosis, ischemic heart disease, chronic obstructive pulmonary disease, malignancy, renal and hepatic failure.[870–872] Improved Survival of this cohort in ICU has resulted from better treatment of HIV and better critical care practices. Fewer than 30% of the admissions to ICU are due to opportunistic infections.[865] Acute respiratory failure, reduced conscious level and bacterial sepsis are the most common causes of admission to ICU, be it HIV infected or non-infected patient. Risk factors for increased mortality in critically ill HIV patients include cART naivety, CD4 lymphocyte counts < 200 mm^3, viral loads ≥ 50 mm^3, HIV-unrelated comorbid disease, malignancies, chronic liver disease and hepatitis C virus infection; high critical illness severity indexes; admission for medical rather than surgical reasons; and a need for invasive mechanical ventilation, vasopressor infusion, renal replacement therapy, thrombocytopenia, length of ICU stay, and severity of illness (high APACHE II or SOFA scores).[873–876]

The HIV Patient in ICU with Acute Respiratory Failure

Respiratory failure is the most important cause of ICU admission among HIV patients.

Recurrent *pneumoniae* in a HIV patient is an AIDS defining condition. The incidence rate of serious bacterial infections was 0.87 per 100 person-years In the Strategic Timing of Anti Retroviral Treatment (START) study, and two-thirds of these infections were due to bacterial *pneumoniae*.[877] The causes of community-acquired *pneumoniae* are like non- HIV patients. The most common pathogens are viral infections, *Pneumocystis jirovecii*, *Streptococcus pneumoniaee*, *H. Influenzae*, M. tuberculosis, *Staphylococcus aureus*, *Klebsiella pneumoniaee*, *Pseudomonas aeruginosa*, and *Escherichia coli* (Table 10).[878–881]

The viral infections such as influenza and covid-19 are associated with higher mortality in HIV patients than non-HIV patients.[882] Antibiotics need to be given for a minimum of 5 days of treatment and may be stopped in case patients remain afebrile for 48 to 72 hours and are clinically stable. TB and PCP are the most common cause of respiratory failure in HIV patients, both accounting for 20% each as causes of respiratory failure in HIV patients. Individuals with HIV remain at higher risk for tuberculosis even with high CD4 counts. Table 11 enumerates risk factors for *pseudomonas* and staphylococcal infections in HIV infected patients.

Pneumocystis jirovecii pneumoniae sets in slowly over weeks with increasing dyspnoea, dry cough and fever. It is treated with 3 weeks of cotrimoxazole (TMP (15–20 mg/kg/day) plus SMX (75–100 mg/kg/day) IV) . Alternative treatment is Pentamidine IV 4

Table 10: Etiology of acute respiratory failure in patients with HIV

Author/Country	*Design*	*Study Population*	*Microbiology*
Pecego et al., Brazil 2020[878]	Prospective observational study	49 patients People living with HIV With without SARI	Respiratory virus (9 SARI vs 13 non-SARI), bacteria (5 SARI vs 4 non-SARI), *Mycobacterium tuberculosis* (6 SARI group vs 7 non-SARI group), *Pneumocystis jirovecii* (4 SARI vs 1 non-SARI), *Cryptococcus neoformans* (1 SARI vs 3 non-SARI), and influenza A (1 SARI vs 2 non-SARI)
Maartens et al., South Africa, 2020[879]	Prospective cohort study	284 HIV-infected inpatients with World Health Organization danger signs and cough	148 culture-positive tuberculosis, 100 had community-acquired *pneumoniae* (CAP), 26 had PCP *Haemophilus influenzae* and *Streptococcus pneumoniaee* were the commonest bacterial pathogens
Elabbadi et al., France, 2020[880]	Bicenter retrospective study	123 episodes of HIV infection in ICU	Rhinovirus was predominant, followed by Influenza and Respiratory Syncytial Viruses. Non-viral copathogen in two-thirds of cases.
Hao et al., China 2023[881]	Retrospective study	231 AIDS adult patients with respiratory failure who were admitted to the ICU	*Pneumocystis jirovecii pneumoniae* (80.1%)

Table 11: Risk factors for *Pseudomonas* and Methicillin resistant Staphylococcal infections

Risk factors for P. aeruginosa	*Risk factors for methicillin-resistant S. aureus*
Advanced immunosuppression/ full blown AIDS (CD4 count ≤50 cells/mm^3)	Recent influenza infection;
underlying structural lung disease such as bronchiectasis	IV drug abusers
Profound neutropenia	Severe, bilateral, necrotizing *pneumoniae*
Treatment with long term corticosteroids	Recent head injury
Severely malnourished patients	Patients on chronic hemodialysis
Those residing in nursing homes/ health care facilities or who had recent hospitalizations in the last 3 months.	
Patients on chronic hemodialysis	

mg/kg/day. Moderate to severe cases (PaO_2 9.3 kPa [70 mmHg] or SpO_2 92%) should be given steroids within 72 hours for mortality benefit and reduction of duration of mechanical ventilation i.e. Prednisone PO 40 mg bid (D1–D5), 40 mg daily (D6–D10) then 20 mg daily (D11–D21), or methylprednisolone IV (75% of prednisone dose). Radiological findings include patchy or diffuse ground-glass opacities and alveolar consolidation with peripheral sparing, reticular infiltrates, intra-parenchymal cysts, without pleural effusion or mediastinal lymphadenopathy.[871,883] Other rare pulmonary opportunistic infections include Kaposi sarcoma (HHV-8 human herpes virus-8), cytomegalovirus, toxoplasmosis, Mycobacterium avium complex, nocardiosis, aspergillosis, rhodococcosis, histoplasmosis, cryptococcosis, *Legionella*, *mycoplasma*, chlamydophila, etc. These are AIDS defining illness which occur when CD4 count falls below 200. Pulmonary TB presents typically as cavitary lesions but in immunocompromised patients may also present as diffuse miliary patterns or in extrapulmonary sites. The treatment remains standard antitubercular drug therapy for 6-12 months i.e., Intensive phase (2 months): isoniazid + rifampin or rifabutin + pyrazinamide + ethambutol and Continuation phase: isoniazid + rifampin or rifabutin.[871] Disseminated Mycobacterium avium complex *(MAC*) disease may present as respiratory failure with diffuse reticulonodular pulmonary infiltrates. This should be treated with clarithromycin (500 mg PO two times daily) or azithromycin (500–600 mg) + ethambutol (15 mg/kg PO daily) for 12 months. Cytomegalovirus (CMV) reactivation is seen in severely immunocompromised patients with HIV (CD4 count <50 cells mm^3) It is characterized by diffuse interstitial pulmonary infiltrates. It is treated with Ganciclovir 5 mg/kg IV q12h. The incidence of bacteremia accompanying *pneumoniae* is greater than in individuals without HIV, especially when infection is due to *S. pneumoniaee*. Predictors of mortality include CD4 count <100 cells/mm^3, radiographic progression of disease, and presence of shock.[871]

Evidence Statement

Respiratory failure is the most important cause of ICU admission among HIV patients. Causes of community-acquired *pneumoniae* are similar to non-HIV patients. However, tuberculosis, and opportunistic infections (like *Pneumocystis Jirovecii*, *cryptococcus*, CMV) are also common, and can present with respiratory failure. Viral infections like influenza and covid-19 are other important causes. Increasing age, comorbidities, severity of illness, extent of organ dysfunction and cART naivety are predictors of increased mortality.

Recommendation

- Patients with severe *pneumoniae* who require intensive care and without risk of *Pseudomonas aeruginosa* should be empirically treated with an IV β-lactam plus IV macrolide (2A). Preferred β-lactams are ceftriaxone, cefotaxime, or amoxicillin-clavulanic acid. In patients who are allergic to penicillin, aztreonam plus azithromycin should be used (3A).
- If patients with HIV/AIDS develop acute respiratory failure and they have any of the risk factors (Table 1) for *Pseudomonas*

infection we recommend dual antipseudomonal coverage such as anti-pseudomonal β-lactam plus aminoglycoside (examples of anti-pseudomonal β-lactams include ceftazidime, cefoperazone, cefoperazone-sulbactam, piperacillin-tazobactam, imipenem-cilastatin, or meropenem (3A).
- In patients who are allergic to penicillin, aztreonam can be used in place of the β-lactam. Combination therapy may be considered with the addition of aminoglycosides or antipseudomonal fluoroquinolones (e.g., levofloxacin, ciprofloxacin) (3A).
- We recommend continuing Azithromycin along with anti-pseudomonal therapy for coverage of atypical pathogens (2B).
- We recommend against using fluoroquinolones empirically to avoid development of drug-resistant TB. Patients should also undergo sputum testing for acid-fast *bacilli* simultaneously if fluoroquinolones are being used (3A).
- In patients who have risk factors for methicillin-resistant *Staphylococcus aureus* (MRSA) infection–empiric treatment should include vancomycin or linezolid (3A).
- Empiric therapy should cover *P. aeruginosa* or MRSA if previously isolated from sputum cultures (3A).
- Steroids are not indicated except in cases of refractory shock (2A).
- We suggest the addition of clindamycin (to vancomycin, but not to linezolid) in cases of severe necrotizing *pneumoniae* to minimize bacterial toxin production (3B).
- Those with CD4 counts <200/mm^3 and without signs of focal consolidation may be suspected to have PCP (2A).
- All diagnosed cases of HIV should receive cART and trimethoprim-sulfamethoxazole (TMP-SMX) for PCP prophylaxis to reduce the risk of *pneumoniae* (1A).
- A switch to oral therapy should be considered in patients with community-acquired *pneumoniae* (CAP) on IV antibiotic therapy who have improved clinically, can swallow, and tolerate oral medications, and have intact gastrointestinal function (2A).
- cART should be initiated promptly within 2 weeks of initiating therapy for the *pneumoniae* if not started (2A).
- Diagnostic work up of acute respiratory failure in HIV patient should consist of: (3A)
  - Complete blood count with CD4 cell count.
  - Sputum microscopy and culture especially for acid fast bacilli (AFB), Nucleic acid amplification tests (NAATs) for TB.
  - Chest imaging, lung ultrasound.
  - Bronchoalveolar lavage (BAL) for culture, staining with Gomori-Grocott or Giemsa or direct fluorescence antibody for PCP, PCR.
  - Blood culture.
  - BAL 1, 3 beta-D-glucan (BDG).
  - Urine antigen for *L. pneumophila* and *S. pneumoniae*.
  - Serum LDH, BDG.
- Rule out non-infectious causes of respiratory failure- COPD, Bronchiectasis, lung cancer, heart failure, lung fibrosis, interstitial pneumonitis, drug toxicity, asthma, pulmonary embolism (3A).

HIV-positive Patient Presenting with Signs of CNS Infection in ICU

Low CD4 counts predispose these patients to infections and development of tumors. The most common focal lesion is toxoplasmosis. In severely immunosuppressed patients with CD4 cell counts <200/mm^3, CNS mass lesions are most common. Common CNS opportunistic infections (OI) are toxoplasmosis, tuberculosis, cryptococcosis Rare CNS OI are CMV, nocardiosis, aspergillosis, PML, HIV encephalitis, NHL, neurosyphilis.

In addition, multiple etiologies can coexist in an immunosuppressed individual.[884–886]

TB meningitis typically presents with fever, focal neurological deficits, progressive cognitive decline and new-onset seizures. CSF suggests lymphocytosis, low glucose and increased protein. NAATs are highly specific. Treatment is as per national guidelines with four or more CNS penetrating drugs along with adjuvant steroid therapy (dexamethasone (0.3–0.4 mg/kg/day for 2–4 weeks, then tapering over 8–10 weeks).[876]

Cerebral toxoplasmosis presents as motor deficit, altered cognition and seizures. It is seen as ring enhancing lesions in brain, mostly in basal ganglia. Evaluation includes PCR for T. gondii on CSF sampling and a positive IgG test. Treatment is with a combination of pyrimethamine and sulfadiazine for 6 weeks or longer, with regular clinical and radiological review to monitor treatment response. Pyrimethamine 200 mg PO once then pyrimethamine 50–75 mg PO daily + sulfadiazine 1000–1500 mg PO q6h + leucovorin 10–25 mg PO daily. Corticosteroids are added to alleviate mass effect. Initial therapy is followed by chronic maintenance therapy by Pyrimethamine 25–50 mg PO daily plus sulfadiazine 2,000–4,000 mg PO daily (in 2–4 divided doses) plus leucovorin 10–25 mg PO daily.

Cryptococcal meningitis usually presents with low-grade fever, worsening headache, seizures, visual symptoms and a progressive cognitive deficit. Diagnosis includes India ink staining for *cryptococcus* and a positive CSF cryptococcal antigen test. MRI of the brain may reveal characteristic encephalitis, hydrocephalus and/or signs of raised intracranial pressure. Treatment includes Induction therapy (> 2 weeks): AmB-L 3–4 mg/kg IV daily plus flucytosine 25 mg/kg qid followed by Consolidation therapy (8 weeks from negative CSF): fluconazole 400 mg daily. For clinically stable patients with negative CSF cultures, dose can be reduced to 400 mg PO once daily and if CSF remains positive after 2 weeks, fluconazole increased to 1200 mg daily. Steroids are not indicated and are associated with worse outcomes. Maintenance therapy is with Fluconazole 200mg PO daily for ≥1 year from initiation of antifungal therapy.

Immune reconstitution inflammatory syndrome (IRIS) is a concern when cART is started in undiagnosed or partially treated opportunistic infection and its incidence is 13%. Paradoxical worsening of treated OIs is called paradoxical IRIS and unmasking of previously subclinical untreated infections is called unmasking IRIS. IRIS is diagnosed when there is a temporal association between starting of cART and development of symptoms within 3 months, evidence of an inflammatory process through clinical signs and symptoms and evidence of immune restoration (virologic and immunologic response). In CNS infections, there may be neurological deterioration after starting cART because of IRIS. Except for the life threatening conditions, cART provides mortality benefit in setting of IRIS and should be continued.[876,883,887]

Steroids should be given in patients with tuberculosis and Mycobacterium avium complex IRIS, but not in IRIS associated with Kaposi sarcoma.[888] Progressive multifocal encephalopathy (PML) is caused by JC virus confirmed with Positive JCV PCR on CSF and presents with demyelinating white matter lesions. The treatment is to initiate or optimize cART. By all means, cART should be continued in the intensive care. Hurdles to implementation of the same are

availability of only enteral medicines, disturbances in gastric pH, renal hepatic dose modifications, drug interactions, etc.[889,890]

Evidence Statement

Patients with HIV and low CD4 counts are prone to opportunistic CNS infections like toxoplasmosis, tuberculosis, cryptococcosis. Less common opportunistic CNS infections are CMV, nocardiosis, aspergillosis, and neurosyphilis. CNS mass lesions and lymphoma are also common with low CD4 counts, Multiple etiologies can often co-exist. Clinical and laboratory evaluation and prompt management is associated with improved outcomes.

Immune reconstitution inflammatory syndrome (IRIS) is another differential if cART is started in undiagnosed or partially treated opportunistic infections.

cART should be continued in the HIV patients admitted to intensive care unit as much as possible.

Recommendation

- For a patient coming to ICU with altered CNS function and suspicion of meningitis, we recommend a third-generation cephalosporin- known to penetrate the blood-brain barrier - at higher doses, e.g., Ceftriaxone 2 gm BD intravenously (1A).
- We suggest the addition of vancomycin empirically to the initial treatment regime (1B).
- We recommend de-escalating antibiotics after culture reports are available (1A).
- In patients above 50 years of age, we suggest the use of additional ampicillin at high doses of 2 gm every 6th hourly (1B).
- In very young infants of age <1 month, we suggest Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside as the initial management (1B).
- Diagnostic work up for CNS infection in HIV patient should consist of (3A):
  - Complete blood count with CD4 cell count.
  - Lumbar puncture, CSF (Cerebrospinal fluid) for cell count, glucose, protein, ADA (Adenosine deaminase), lactate, culture, PCR.
  - For immunocompromised host-*Toxoplasma gondi* IgG antigen and antibodies, cryptococcal antigen (serum and CSF).
  - Brain imaging preferably MRI (Magnetic resonance Imaging).

HIV-positive Patients Presenting with Suspected Bloodstream Infections or Sepsis of Unknown Origin

Lack of cART, low CD4 count, alcohol abuse, smoking, and comorbidities such as liver disease are risk factors associated with bacteremia.[891] The common organisms seem to be non-typhoid Salmonellae, *Streptococcus pneumoniaee*, *Escherichia coli*, *Staphylococcus aureus*, and coagulase-negative Staphylococci (Table 12).[889,892–897] Undifferentiated fever in patients with low CD4 counts may be due to viral syndromes such as CMV, Disseminated *mycobacteria*l disease, disseminated fungal disease (cryptococcal disease, etc. Non-infectious etiologies should also be kept in mind such as drug reactions, malignancy, hemophagocytic lymphohistiocytosis (HLH) or IRIS, etc. Septic shock and multiorgan failure may occur during the course of disseminated OIs like toxoplasmosis, tuberculosis, and histoplasmosis. These infections commonly trigger hemophagocytic lymphohistiocytosis. Drug-resistant organisms are also seen more commonly in HIV patients. In the absence of any localizing symptoms, the diagnostic work up should include bacterial blood cultures, a serum cryptococcal antigen, fungal markers, such as a BDG, serum or urine *Histoplasma* antigen, *Coccidioides*-specific antigen testing, CMV viral load, *mycobacteria*l isolator blood cultures.[868] HIV patient with high CD4 count, undetectable viral load and adherence to cART, the differential diagnosis of any critical illness will be similar to non-HIV patient as both are immunologically similar. There is evidence that in-hospital mortality in HIV patients depends on age, underlying comorbidities and extent of organ dysfunctions and not HIV related parameters such as viral load, CD4 cell count, admission for AIDS-related diagnoses, and prior cART use.[871]

Evidence Statement

Lack of cART, low CD4 count, alcohol abuse, smoking, and comorbidities such as liver disease are risk factors associated with bacteremia in HIV patients, Common organisms seem to be non-typhoid Salmonellae, *Streptococcus pneumoniaee*, *Escherichia coli*, *Staphylococcus aureus*, and coagulase-negative Staphylococci. Undifferentiated fever in patients with low CD4 counts may be due to viral syndromes such as CMV, Disseminated *mycobacteria*l disease, disseminated fungal disease or noninfectious etiology. Disseminated opportunistic infections may trigger hemophagocytic

Table 12: Common organisms isolated from the bloodstream in patients with HIV

Author/Country	*Design*	*Study Population*	*Microbiology*
Michaëla et al., Netherland 2014[892]	Systematic literature review.	Hospitalized patients	Nontyphoid salmonellae (NTS), *Streptococcus pneumoniaee*, *Escherichia coli*, and *Staphylococcus aureus*
Nadjm et al., Rural Tanzania 2012[893]	Prospective observational study and cohort study	Fever and 1 severity criterion	NTS 3 (25), *S. pneumoniaee* 3 (25), *Streptococcus pyogenes* 2 (17)
Kiertiburanakul et al., Thailand 2012[894]	Retrospective observational study	BSI in HIV patients	*Salmonella* spp. 21 (26), *E. coli* 14 (18), *S. aureus* 12 (15)
Phe et al., Cambodia 2013[895]	Retrospective study using prospectively collected data	435 patients community-acquired BSI	*E. coli* 27 (31), *S. aureus* 17 (19), NTS 16 (18)
Barr et al., 2020[896]	Meta-analysis, 23 datasets	5751 seriously ill patients	M. tuberculosis BSI is a frequent manifestation of tuberculosis and predicts mortality (adjusted hazard ratio 2.48)
Qi et al., China 2016[897]	Retrospective cross-sectional study	2442 Chinese HIV-seropositive inpatients, 229 (9.38 %) experienced BSIs	*Cryptococcus neoformans* (22.7%), Penicillium marneffei (18.8%), *Mycobacterium tuberculosis* (15.3%), and non-tuberculous mycobacterium (14.8%)

lymphohistiocytosis. Drug-resistant organisms are also seen more commonly in HIV patients. Extensive diagnostic work up is needed in HIV patients with sepsis of unknown origin. In-hospital mortality in HIV patients depends on age, underlying comorbidities and extent of organ dysfunctions and not HIV related parameters such as viral load, CD4 cell count, admission for AIDS-related diagnoses, and prior cART use.

Recommendation

- In the presence of sepsis or septic shock, we recommend following the surviving sepsis guidelines like the management of other patients with sepsis (UPP).
- In the absence of septic shock or absence of risk factors for *Pseudomonas* a monotherapy with a third-generation cephalosporin or a cephalosporin, the b-lactamase inhibitor is sufficient (2A).
- In more severe disease states, such as in the presence of organ dysfunction or septic shock–a combination of broad-spectrum antibiotics may be used for initial empiric therapy (3A).
- Empiric gram-positive coverage is suggested for those who have risk factors for MRSA (UPP).
- Anti-fungal agents may be considered only if there is no clinical improvement or there is clinical deterioration even after 72 hours of appropriate empirical antibiotics therapy and CD4 counts $<200/mm^3$ (2A).
- We recommend against the use of routine empirical antifungal therapy (2A).

Congenital and Acquired Hyposplenism and Asplenia

Spleen is secondary lymphoid organ which filters organisms from the blood and also regulates immune response. Patients with congenital and acquired hyposplenism/asplenia are prone for specific infections, particularly by encapsulated bacteria (namely, *Neisseria meningitidis*, *Streptococcus pneumoniaee*, *Haemophilus influenzae* type b). These patients are at increased risk of severe sepsis. Asplenia is predominantly due to splenectomy for either traumatic events or onco-hematological conditions. Although the incidence of sepsis remains low, the risk for overwhelming post-splenectomy infection (OPSI) is higher than in the general population.[898] Even if most post-splenectomy infections (OPSI) are caused by encapsulated bacteria, other infections can also occur.[899,900] The infection starts as a minor flu-like illness and rapidly evolves into a fulminant course of hypoglycemia, metabolic acidosis, dyselectrolytemia, disseminated intravascular coagulation (DIC), shock, coma and death within 24 to 48h.[901] OPSI usually occurs within the first two years after splenectomy but may also occur later and has a mortality rate of 50%-70% despite aggressive therapy.[899] In view of the severe progression and high mortality of OPSI, stress has been given for early aggressive treatment as well as immunization of patients with splenectomy and thereby preventing OPSI.

What Should be the Approach to Empiric Therapy in Patients with Hyposplenism or Asplenia who Develop Sepsis?

Splenectomy is often performed in patients with an underlying malignant or nonmalignant hematologic disease or in patients with splenic rupture after trauma or infection. Rarely there may be congenital absence of spleen. Other causes of hyposplenia include auto infarction in subjects with sickle cell anemia and chronic graft-versus-host disease after stem-cell transplantation, severe celiac disease, and untreated human immunodeficiency virus infection.[902]

Overwhelming post-splenectomy infection (OPSI) is defined as an infection, occurring more commonly after splenectomy (or in hyposplenic host) which evolves over a short time and produces severe symptoms, often with hypotension and a high mortality rate.[903]

Patients with hyposplenism due to splenectomy or hyposplenia are at an increased risk for invasive infections with encapsulated bacteria as *Streptococcus pneumoniaee*, *Haemophilus influenzae* type b, *Neisseria meningitidis*.[899,904] Some splenic function may be preserved in post-splenectomy patients due to seeding of the peritoneum due to rupture or intentional implantation of splenic tissue performed during elective surgery. These infections progress rapidly from a mild flu-like illness to fulminant sepsis and are associated with a high mortality rate of up to 50% despite maximal treatment. The lifetime risk of OPSI is assumed to be 5%, and the highest frequency of these OPSI is during the first 2 years after splenectomy.[903,905,906] Patients with sickle cell anemia, thalassemia major or malignancies such as Hodgkin's lymhomas and non-Hodgkin's lymphomas have a higher risk for OPSI. Asplenic patients have a higher incidence of parasitemia, a delayed clearance of parasites after treatment or a severe or even fatal infection due to malaria. These patients are also at high risk for Babesiosis and this might be confused with *Plasmodium falciparum*.[899] These patients are at an increased risk of OPSI with *Capnocytophaga canimorsus*, if bitten by dogs and other animals and should receive adequate antibiotic coverage following such bites.[907] Otherwise rare, Ehrlichiosis is also more severe in patients with asplenia/hyposplenia.[899]

OPSI should be considered as a medical emergency and mandates early recognition and aggressive management. These patients should be managed aggressively including immediate cultures and administration of a combination of antibiotics to cover all possible etiological agents. In areas where penicillin-resistant pneumococci are prevalent, other agents such as vancomycin, teicoplanin or rifampicin should be added to ceftriaxone as the initial empiric therapy. Gram stain of the peripheral blood or buffy coat will give an idea regarding the presence or absence of intraleukocytic bacteria. Anti-pseudomonal coverage should be added in case of high risk for *pseudomonas* infection or peripheral blood growing GNB. The presence of intracellular bacteria within leukocytes should alert the clinician towards ehrlichiosis while the presence of parasites in RBC should alert for malaria or babesiosis. Once the blood cultures are positive antibiotics can be modified accordingly.

Evidence Statement

Patients with congenital and acquired hyposplenism/asplenia are at high risk for encapsulated bacterial infections like *Neisseria meningitidis*, *Streptococcus pneumoniaee* and *Haemophilus influenzae* type b. These patients are more likely to have severe sepsis, and overwhelming post-splenectomy infection (OPSI). OPSI can present with flu-like illness at onset, and rapidly progress to septic shock and death, and therefore needs prompt institution of antibiotics covering for both gram-positive and gram-negative organisms under close observation in high dependency or intensive care units.

Recommendation

- If an asplenic or hyposplenic patient is suspected to have sepsis we recommend administration of IV ceftriaxone before transferring the patient to a higher center (2A).
- We recommend that all patients with Overwhelming Post-Splenectomy Infection (OPSI) be treated in the ICU (UPP).
- We recommend empiric antibiotic therapy for asplenic patients with a combination of ceftriaxone and vancomycin (1A).
- In case of allergy to β-lactams, we recommend vancomycin with aztreonam or fluoroquinolones in adults. Do not delay administration of antibiotics, be prepared to treat reaction (UPP).
- We recommend to add clarithromycin or erythromycin in case of respiratory symptoms (3A).
- We recommend empiric therapy with IV Cefotaxime + vancomycin+ ampicillin, if the patient age <2 months (3A).
- All febrile asplenic patients should be screened for malaria with peripheral smears. Start artesunate based antimalarial therapy, if the history is suggestive of Malaria (UPP).
- If gram staining of peripheral blood smear shows gram-negative bacilli, we recommend addition of antipseudomonal coverage to the therapy (3A).
- We recommend that urine be checked for urinary antigen for *streptococcus pneumoniae* (2A).
- We suggest RT-PCR test for simultaneous identification of 3 main encapsulated bacteria (*Str pneumoniae*, *H. influenzae* type B and *N. meningitidis*) (3B).
- We recommend that all asplenic patients should receive immunization against encapsulated bacteria (*S. pneumoniae*e, *H. influenzae*, and *N. meningitidis*) (1A).
- Immunization against seasonal flu is recommended for patients over 6 months of age (1A).
- Vaccination programs should be started no sooner than 14 days after splenectomy (1A).
- If the patient is discharged before 15 days after splenectomy or angioembolization, where the risk to miss vaccination is deemed high, we suggest that patient be vaccinate before discharge (1B).
- Antibiotic prophylaxis is indicated in patients for 1–2 years after splenectomy and lifelong for patient had an episode of overwhelming infection or immunocompromised (2B).
- We recommend self-administration of one dose of, in stock "pill in pocket", prescribed antibiotics in the event of any sudden onset of unexplained fever, malaise, chills or other constitutional symptoms, when medical consultation not readily accessible within 2 hours (2A).
- We suggest that any patient with sepsis having risk factor for hyposplenia, the peripheral smear should be checked for Howell-Jolly bodies (2B).
- We recommend formulation of Spleen registry (UPP).

Patients with Primary Immune Deficiency in the ICU

Primary immunodeficiencies is group of disorders that affect the development, function or both of the immune system. There are more than 300 disorders defined till date. The prevalence is approximately 1 in 10,000 live births.[692,908,909] Any patient admitted to ICU could be a potential PID patient.

Diagnosis of PID

Diagnosis is often delayed since signs and symptoms such as bronchitis, *pneumoniae*, sinusitis, diarrhea are considered infection related without suspecting immunological process.

Table 13: Absolute Lymphocyte count (ALC) nomoGram

Age	*Lymphocytes (per mm^3)*	*Range (per mm^3)*
Neonatal	4.8	0.7–7.3
1 month– 2 month	6.7	3.5–13.1
2–5 months	5.9	3.7–9.6
5–9 months	6.0	3.8–9.9
9–15 months	5.5	2.6–10.4
15–24 months	5.6	2.7–11.9
2–5 years	3.3	1.7–6.9
5–10 years	2.8	1.1–5.9
10–16 years	2.2	1.0–5.3
>16 years	1.8	1.0–2.8

Any value below the reference range should raise suspicion of PID

The absence of adenoid tissue in the nasopharynx or absence of the thymus should prompt suspicion of primary immunodeficiency (antibody or cellular/combined).

The presence of lymphocytopenia on complete blood count suggests a T-cell disorder, whereas a finding of neutropenia suggests a phagocytic disorder. Abnormal serum immunoglobulin levels suggest a B-cell disorder. Abnormalities on assay of the classic or alternative complement pathways suggest a complement disorder.[910] Abnormal values of lymphocyte count should also raise suspicion of PID (Table 13).

Patients with PID commonly present with recurrent infections and invasive infections, atypical pathogens, partial response to antibiotics, failure to thrive, chronic diarrhea, fungal infections, unexplained skin rash and a family history. Infections such as *Pneumoniae* and bronchiolitis, acute gastroenteritis, otitis media, and bacteremia in patients with antibody, combined, and cellular deficiencies. Whereas viral infections meningitis, osteomyelitis, gastroenteritis is commonly seen in CVID. Children tend to have bacterial or fungal infections with unusual organisms, or unusually severe and recurrent infections with common organisms. A family history of primary immunodeficiency disease is the strongest predictor of a person having this type of disease.[911]

The typical presentations of various PIDs by age of presentation and spectrum of infections.

1. Combined T-cell and B-cell immunodeficiency (Presents early in life)
   a) Bacteria: *Campylobacter Listeria*, *Pyogenic bacteria*, *Mycobacteria*
   b) Viruses: RSV, EBV, Parainfluenza Virus
   c) Fungi: *Candida*, *Aspergillus*
   d) Protozoa: *Pneumocystis jirovecii*, *Toxoplasma Gondi*, *Cryptosporidium parvum*
2. B cell immunodeficiency (Presents when weaning is started and breast feeding stops)
   a) Bacteria: *S. pneumoniae*, *H. influenza*, *M. catarrhalis*, *P. aeruginosa*, *S. aureus*, *N. meningitidis*, *M. pneumoniae*
   b) Viruses: Enteroviruses
   c) Protozoa: Giardia lamblia
3. Congenital defects of phagocyte number and function (Can present at any age based on severity of the defect)
   a) Bacteria: *S. aureus*, *P. aeruginosa*, *Nocardia*, *S. typhi*

Table 14: The types of clinical patterns of presentation and infections in PIDs

Immunodeficiency	*Infections*	*Example*
Antibody deficiency Phagocyte deficiency Complement deficiency	Bronchiectasis, rhino sinusitis	HIV, Wiskott-Aldrich Syndrome
T-lymphocyte deficiency	Chronic diarrhea, *Candida*/ PCP, *Mycobacteria*	SCID/HIV
Neutrophil defects	Recurrent pyogenic infections, Invasive *Aspergillus*, *Burkholderia*	Chronic granulomatous disease (CGD)
Defects of innate immunity(TLR3)	Invasive pneumococcal disease	SCID/HIV
T-lymphocyte deficiency	Herpes Simplex Encephalitis	Wiskott-Aldrich Syndrome
T-lymphocyte/macrophage deficiency	Meningococci, encapsulated bacteria or *Candida*/ *Mycobacteria*	
Common variable immunodeficiency (CVID)	Autoimmune or chronic inflammatory disease	Hemophagocytic lymphohistiocytosis (HLH)

In ICU setting in patients with PID; following organisms are likely to cause infections

   b) Fungi: *Candida*, *Aspergillus*
   c) *Mycobacteria*: Nontuberculous including BCG
4. Complement deficiencies (Can present as early as within 6 months of life)
   a) Bacteria: *Streptococci*, *H. influenza*, *Neisseria*,
   b) Viruses: CMV, HSV

The European Society for Immunodeficiency (ESID) clinical guidelines[912] proposed the grouping of immunodeficiency, syndromes and likely infections as follows (Table 14).

1. B cell deficiency
   a) Pneumococcus
   b) *H. influenza*
   c) Staph Aureus
   d) Giardia Lamblia
   e) Viruses Enterovirus/echovirus
2. T cell deficiency
   a) *Mycobacteria*
   b) Viruses- CMV/EBV/HSV/RSV/VZ/Parainfluenza
   c) Fungi- *P. carini*, *Histoplasma*, *cryptosporidium*, *Toxoplasma*
3. Phagocytic disorder
   a) Gram-negative: *E. coli/Klebsiella/B. cepacia/Pseudomonas/ Serratia*
   b) Gram-positive: Staph/*Nocardia*/ *Listeria*
   c) Fungus: *Aspergillus* and *Candida*
4. Defects in the complement system: *Streptococcus pneumoniae* and *Neisseria*
5. Mendelian susceptibility to mycobacterium (MSMD): *Mycobacteria*, *salmonella typhi* and nontyphii, *Listeria*, viral and other intracellular pathogens (e.g., *Histoplasma*, leishmania)[913–918]

The data regarding the use of Antibiotics in Immunodeficiency states is scarce. The experts recommend using antibiotic as per organism isolated or expected. Generally the management depends upon the type of PID.

Therapy includes:

1. IV Immunoglobulin (IVIG) infusion mainly for B cell deficiency[919–921]
2. Antibiotics as per suspected source of infection and suspected organism
3. Rituximab in PID with Epstein Barr virus reactivation

Stem cell transplant is the most curative option for majority of the PID. Paradoxically Rituximab treatment has known to aggravate primary immunodeficiency or hypogammaglobulinemia in certain group of patients and appropriate care has to be taken in these patients. In PID such as X-linked Lymphoproliferative disorder, Rituximab can be given once in 4 weeks to decrease the EBV Viral load.[692,908,910]

Evidence Statement

A diagnosis of primary immunodeficiency should be considered in patients with serious infections. Significant family history, hematologic abnormalities like neutropenia, lymphopenia, recurrent infections, or infections with uncommon organisms can lead to evaluation for primary immunodeficiency. Recurrent sinopulmonary infections are seen with humoral immunodeficiencies. Recurrent infections with organisms like tuberculosis or endemic fungi should lead to evaluation for cell mediated immunodeficiency. Microbiologic diagnosis is important in patients with suspected immunodeficiency due to higher incidence of co-infections and drug resistant infections. In patients with primary immunodeficiency with serious infections, empiric coverage for causative organisms, including viruses and invasive fungal infections is practiced. Treatment for underlying immunodeficiency (e.g., intravenous immunoglobulin therapy) and comorbid autoimmune conditions improves outcomes.

Recommendations

- PID should be suspected when the following history/symptoms or signs are present (UPP):
  - Family history of sibling death.
  - Four or more ear infections within 1 year.
  - Two or more serious sinus infections or *pneumoniae*s within 1 year.
  - Two or more months on antibiotics with little effect.
  - Two or more deep seated infections including septicemia.
  - Persistent thrush in mouth or fungal infection on skin.
  - Infections in multiple anatomic locations.
  - Increasing frequency and severity of infections with age.
  - Recurrent serious infections with common pathogens.
  - Serious infections with unusual pathogens.

- We recommend that when PID is suspected, HIV infection should also be considered, and testing should be performed for HIV (UPP).
- We recommend that patient should be investigated for PID when: (3A)
  - In neonates, Absolute Lymphocyte count (ALC) of <2000/mm^3 in cord blood or in an infant an ALC of <4000/mm^3.
  - Severe hypogammaglobulinemia with IgG <1 50mg/dL.
  - Absolute Lymphocyte count <4000/mm^3 (In non-chemotherapy setting).
  - Unusual organism picked up on microbiology.
  - Unexplained neutropenia.
- We recommend that Initial laboratory screening should include a complete blood count with differential counts (including Absolute Lymphocyte Count, Absolute Neutrophil Count, Absolute Monocyte Count) and measurement of serum immunoglobulin and complement levels (UPP).
- We recommend Severe Combined Immune deficiency (SCID) be considered as a pediatric emergency and attention be paid to Absolute Lymphocyte Count, at all time in ICU. If the Absolute Lymphocyte Count is less than normal for the age, we recommend to take immunology reference, use irradiated blood products, and avoid live vaccines till diagnosis is confirmed or ruled out (UPP).
- We recommend that patient be investigated for Combined Variable Immuno-deficiency (CVID) when patient has any of the following (UPP):
  - Recurrent bacterial infections.
  - Serum IgG, IgM, IgA levels (at least two of the three) with a marked decrease (at least 2 SD below the mean for age).
  - Onset of immunodeficiency at more than 2 years of age.
  - Absence of isohemagglutinins and or poor response to vaccines.
- We recommend that immunology consult be obtained for these patients and the patient be investigated to diagnose specific form of immunodeficiency (UPP)
  - Lymphocyte subpopulations by Flow cytometry (CD3, CD4, CD8, CD19, CD20, CD16 & CD56).
  - Naive T cells, Memory B cells, Memory T cells
  - T-cell response to mitogens.
  - Nitroblue Tetrazolium-NBT test
  - Complement levels
  - Bone Marrow and Genetic tests
- We recommend for all critically ill patients with suspicion of PID the empirical antimicrobial treatment with IV Carbapenems with IV Vancomycin/Teicoplanin for broad-spectrum coverage.(UPP, A). Voriconazole is the preferred antifungal in case of proven, possible or probable invasive fungal infection with *aspergillus* (IA).
- In critically ill patients diagnosed with Combined B and T cell deficiency the antimicrobial drug of choice is IV Carbapenems with Vancomycin/Teicoplanin and Trimethoprim-Sulfamethoxazole (UPP).
- In critically ill patients diagnosed with Combined B and T cell deficiency with suspicion of viral infections, we recommend (UPP):
  - IV Acyclovir if herpes group of infection is suspected
  - Oral oseltamivir if influenza virus is suspected
  - IV Ganciclovir if CMV is suspected radiologically or by laboratory tests
- In critically ill patients diagnosed with B cell deficiency, based on the organisms expected (Capsulated), we recommend IV ceftriaxone with IV Vancomycin/Teicoplanin (UPP).
- We recommend IV Immunoglobulin (IVIg) at dose of 1 gm/kg weekly in cases of severe infections especially ECHO/Enterovirus / Polio virus induced encephalitis (UPP).
- In critically ill patients diagnosed with Phagocyte disorder we recommend.
- antimicrobial drug of choice to be IV Carbapenems with IV Vancomycin/Teicoplanin and Voriconazole (UPP).
- We Recommend the use of Granulocyte colony stimulating factor (GCSF) in patients of congenital Neutropenia (UPP).
- In critically ill patients diagnosed with complement deficiency the antimicrobial drug of choice is IV Cephalosporin (UPP).
- We recommend appropriate cultures, and PCRs; for organisms likely to cause infections pertinent to the conditions they are suffering from (UPP).
- Attempt should be made to identify the microorganisms directly or on PCRs as serological tests in infectious diseases could give false-negative results if there is an antibody defect (UPP).
- We recommend the use of Multiplex PCR to help diagnose infections (UPP).
- We recommend intravenous Immunoglobulin for treatment of all antibody deficiency diseases, at doses of 400 mg/kg/doses every 4 weekly. We recommend 2 gm/kg single dose (Severe Infections) or 1 gm/kg weekly till infection subsides (UPP).
- We recommend to maintain serum IgG trough levels above 500mg/dl and above 700 mg/dL in bronchiectasis (3A).
- We recommend thoracic computed axial tomography, lung function tests with spirometry and DLCO every 6 months after discharge (UPP).
- We recommend hematopoietic stem cell transplantation in cellular and macrophage immunodeficiency (UPP).
- We recommend monoclonal antibodies such as rituximab only in autoimmune complications related to CVID (UPP).
- We recommend Rituximab be given in PID complicated with EBV viremia (UPP).

What Should be the Approach to Vaccinations and Antimicrobial Prophylaxis at Discharge for Patients with Primary Immunodeficiency Requiring Intensive Care?

Vaccine recommendations should be earmarked only for patients certain PID. Live vaccines are avoided in patients with severe B- and T-cell dysfunction due to the risk of dissemination and the futility of immune response. All vaccines are safe and effective in the patients with complement deficiency(susceptibility to encapsulated organisms).[922–924]

Evidence Statement

Live vaccines are contraindicated in SCID whereas all vaccines are safe and effective in complement deficiency. Antifungal prophylaxis and PCP prophylaxis are important to prevent invasive life-threatening infections in patients with PID.

Recommendations

- All forms of live vaccines, viral and bacterial, are contraindicated in patients with SCID (UPP).
- We recommend vaccination for diagnosed patients with complement deficiency at time of discharge (UPP).

- We recommend avoiding BCG vaccination in Chronic Granulomatous Disease /MSMD patient (UPP).
- We recommend antifungal and anti PCP prophylaxis for all patients diagnosed with PID shifted from ICU (UPP).
- PID patients with chronic granulomatous disease should be treated with Itraconazole (IA) and Trimethoprim-Sulfamethoxazole (2A).
- PCP prophylaxis should be given to all patients with Combined B and T or T cell deficiency with drug of choice being Trimethoprim-Sulfamethoxazole (1A).
- We recommend antifungal prophylaxis in all patients with T cell defects (3A).

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