Guidelines for diagnosis and management of community- and hospital-acquired pneumonia in adults: Joint ICS/NCCP(I) recommendations

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SYNOPSIS OF RECOMMENDATIONS

Diagnosis and management of community-acquired pneumonia (CAP)

What is the role of chest radiograph in the diagnosis of CAP?

1. Wherever feasible, a chest radiograph should be obtained in all patients suspected of having CAP (1A).
2. In the absence of availability of chest radiograph, patients may be treated on the basis of clinical suspicion (3A).
3. Chest radiograph should be repeated if the patient is not improving and also for all those patients who have persistence or worsening of symptoms/physical signs or those in whom an underlying malignancy needs to be excluded. It is not routinely necessary to repeat a chest radiograph in patients who have improved clinically (2A).

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What is the role of computed tomography (CT) in the diagnosis of CAP?

1. CT of the thorax should not be performed routinely in patients with CAP (2A).
2. CT of the chest should be performed in those with non-resolving pneumonia and for the assessment of complications of CAP (2A).

Which microbiological investigations need to be performed in CAP?

Blood cultures

1. Blood cultures should be obtained in all hospitalized patients with CAP (2A).

2. Blood cultures are not required in routine outpatient management of CAP (2A).

Sputum Gram stain and cultures

1. An initial sputum Gram stain and culture (or an invasive respiratory sample as appropriate) should be obtained in all hospitalized patients with CAP (2A).
2. Sputum quality should be ensured for interpreting Gram stain results (2A).
3. Sputum for acid-fast bacilli (AFB) should be obtained as per RNTCP guidelines for non-responders (UPP).

Pneumococcal antigen detection

Pneumococcal antigen detection test is not required routinely for the management of CAP (2A).

Pneumococcal PCR

Pneumococcal PCR is not recommended as a routine diagnostic test in patients with CAP (1A)

Legionella antigen detection

Legionella urinary antigen test is desirable in patients with severe CAP (1B).

Other atypical pathogens

Investigations for atypical pathogens like *Mycoplasma*, *Chlamydia*, and viruses need not be routinely done (2A).

What general investigations are required in patients with CAP?

1. For patients managed in an outpatient setting, no investigations are routinely required apart from a chest radiograph (3A).
2. Pulse oximetry is desirable in outpatients (2B).
3. Pulse oximetric saturation, if available, should be obtained as early as possible in admitted patients (2A). Arterial blood gas analysis should be performed in those with an oxygen saturation ≤90% and in those with chronic lung disease (3A).
4. Blood glucose, urea, and electrolytes should be obtained in all hospitalized patients with CAP (3A).
5. Full blood count and liver function tests are also helpful in the management of patients with CAP (3B).

What is the role of biomarkers in the diagnosis of CAP?

Procalcitonin and CRP measurement need not be performed as routine investigations for the diagnosis of CAP (2A).

Should patients with CAP be risk stratified? What should be the optimum method of risk stratification?

1. Patients with community-acquired pneumonia should be risk stratified (1A).
2. Risk stratification should be performed in two steps [Figure 1] based upon the need for hospital admission followed by assessment of the site of admission (non-ICU vs. ICU). Accordingly, patients can be managed as either outpatient or inpatient (ward or ICU) (1A).
3. Initial assessment should be done with CRB-65. If the score is >1, patients should be considered for admission (1A).
4. Clinical judgment should be applied as a decision modifier in all cases (3A).
5. Pulse oximetry can be used to admit hypoxemic patients (2A). Hypoxemia is defined as pulse oximetric saturation ≤92% and ≤90% for age ≤50 and >50 years, respectively (3A).
6. Patients selected for admission can be triaged to the ward (non-ICU)/ICU based upon the major/minor criteria outlined in Table 6 (2A).
7. If any major criterion or ≥3 minor criteria are fulfilled, patients should generally be admitted to the ICU (1A).

What practices are recommended regarding use of antibiotics in CAP?

Antibiotics should be administered as early as possible; timing is more important in severe CAP (2A).

What should be the antibiotic therapy in the outpatient setting?

1. Therapy should be targeted toward coverage of the most common organism, namely *Streptococcus pneumoniae* (1A).
2. Outpatients should be stratified as those with or without comorbidities (3A).
3. Recommended antibiotics [Table 10] are oral macrolides (e.g. azithromycin) or oral β-lactams (e.g. amoxicillin 500–1000 mg thrice daily) for outpatient without comorbidities (1A).

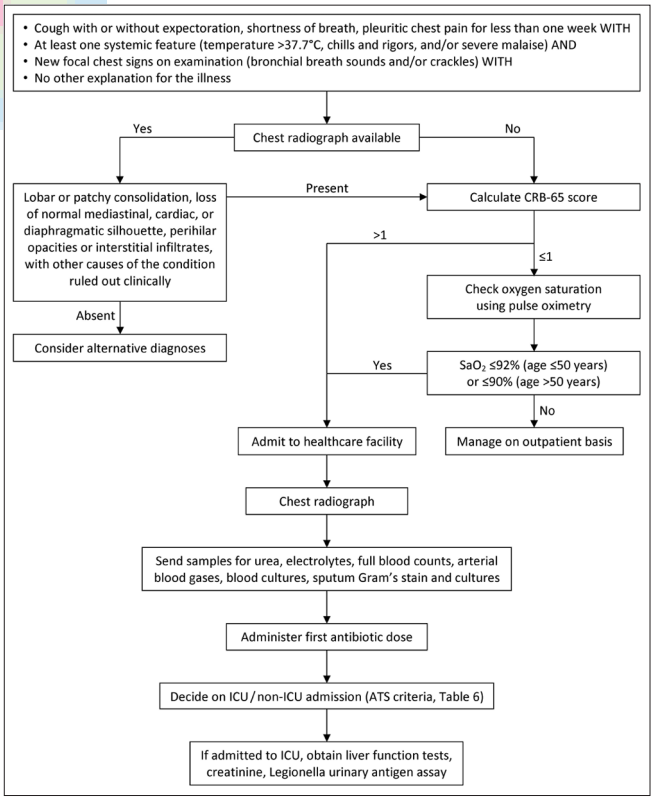

Figure 1: Algorithmic approach to diagnosis and management of CAP (ARDS, acute respiratory distress syndrome; CXR, chest radiograph; ICU, intensive care unit; LFTs, liver function tests; SaO2, arterial saturation)

4. For outpatients with comorbidities [Table 8], oral combination therapy is recommended (β-lactams plus macrolides) (1A).
5. There is insufficient evidence to recommend tetracyclines (3B).
6. Fluoroquinolones should not be used for empiric treatment (1A).
7. Antibiotics should be given in appropriate doses to prevent emergence of resistance (1A).

What should be the antibiotic therapy in the hospitalized non-ICU setting?

1. The recommended regimen is a combination of a β-lactam plus a macrolide (preferred β-lactams include cefotaxime, ceftriaxone, and amoxicillin–clavulanic acid) (1A).
2. In the uncommon scenario of hypersensitivity to β-lactams, respiratory fluoroquinolones (e.g. levofloxacin 750 mg daily) may be used if tuberculosis is not a diagnostic consideration at admission (1A). Patients should also undergo sputum testing for acid-fast bacilli simultaneously if fluoroquinolones are being used in place of β-lactams.
3. Route of administration (oral or parenteral) should be decided based upon the clinical condition of the patient and the treating physician's judgment regarding tolerance and efficacy of the chosen antibiotics (3A).
4. Switch to oral from intravenous therapy is safe after clinical improvement in moderate to severe CAP (2A).

What should be the antibiotic therapy in ICU setting?

1. The recommended regimen is a β-lactam (cefotaxime, ceftriaxone, or amoxicillin–clavulanic acid) plus a macrolide for patients without risk factors for *Pseudomonas aeruginosa* (2A).
2. If *P. aeruginosa* is an etiological consideration, an antipneumococcal antibiotic (e.g. cefepime, ceftazidime, cefoperazone, piperacillin–tazobactam, cefoperazone–sulbactam, imipenem, or meropenem) should be given (2A). Combination therapy may be considered with addition of aminoglycosides/antipseudomonal fluoroquinolones (e.g. ciprofloxacin) (3A). Fluoroquinolones may be used if tuberculosis is not a diagnostic consideration at admission (1A). Patients should also undergo sputum testing for acid-fast bacilli simultaneously if fluoroquinolones are being used.
3. Antimicrobial therapy should be changed according to specific pathogen(s) isolated (2A).
4. Diagnostic/therapeutic interventions should be done for complications, e.g. thoracentesis, chest tube drainage, etc. as required (1A).
5. If a patient does not respond to treatment within 48–72 h, he/she should be evaluated for the cause of non-response, including development of complications, presence of atypical pathogens, drug resistance, etc. (3A).
6. Switch to oral from intravenous therapy is safe after clinical improvement in moderate to severe CAP (2A).

When should patients be discharged?

1. Patients can be considered for discharge if they start accepting orally, are afebrile, and are hemodynamically stable for a period of at least 48 h (2A).
2. Outpatients should be treated for 5 days and inpatients for 7 days (1A).
3. Antibiotics may be continued beyond this period in patients with bacteremic pneumococcal pneumonia, *Staphylococcus aureus* pneumonia, and CAP caused by *Legionella pneumoniae* and non-lactose fermenting Gram-negative bacilli (2A). Antibiotics may also be continued beyond the specified period for those with meningitis or endocarditis complicating pneumonia, infections with enteric Gram-negative bacilli, lung abscess, empyema, and if the initial therapy was not active against the identified pathogen (3A).

What is the role of biomarkers in the treatment of CAP?

Biomarkers should not be routinely used to guide antibiotic treatment as this has not been shown to improve clinical outcomes (1A).

What adjunctive therapies are useful for the management of CAP?

1. Steroids are not recommended for use in non-severe CAP (2A).
2. Steroids should be used for septic shock or in ARDS secondary to CAP according to the prevalent management protocols for these conditions (1A).
3. There is no role of other adjunctive therapies (anticoagulants, immunoglobulin, granulocyte colony-stimulating factor, statins, probiotics, chest physiotherapy, antiplatelet drugs, over-the-counter cough medications, β_2 agonists, inhaled nitric oxide, and angiotensin-converting enzyme inhibitors) in the routine management of CAP (1A).
4. CAP-ARDS and CAP leading to sepsis and septic shock should be managed according to the standard management protocols for these conditions (1A).
5. Noninvasive ventilation may be used in patients with CAP and acute respiratory failure (2A).

What is the role of immunization and smoking cessation for the prevention of CAP?

1. Routine use of pneumococcal vaccine among healthy immunocompetent adults for prevention of CAP is not recommended (1A). Pneumococcal vaccine may be considered for prevention of CAP in special populations who are at high risk for invasive pneumococcal disease [Table 11] (2A).
2. Influenza vaccination should be considered in adults for prevention of CAP (3A).
3. Smoking cessation should be advised for all current smokers (1A).

Diagnosis and management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP)

What is the utility of healthcare-associated pneumonia (HCAP)?

The risk stratification regarding acquisition of MDR pathogen should be individualized rather than using an

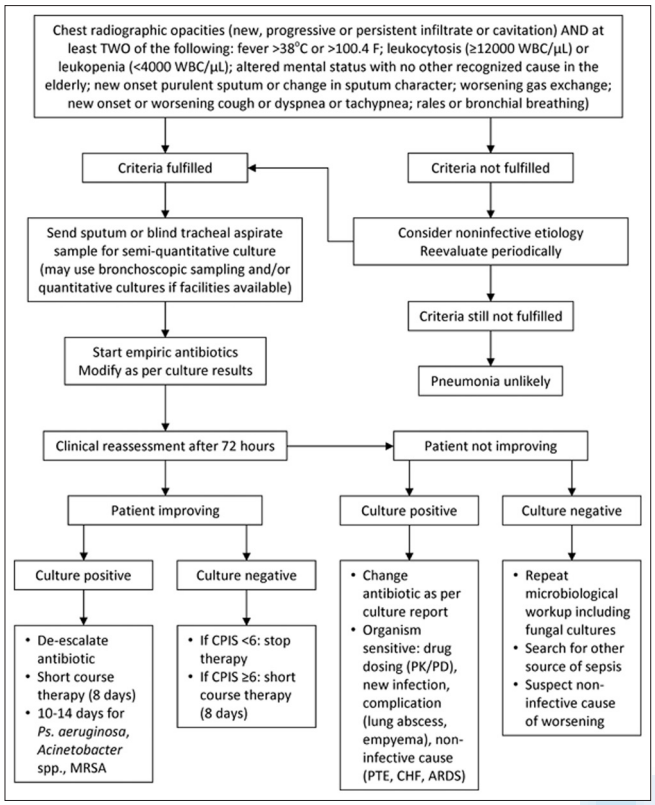

Figure 2: Algorithmic approach to diagnosis and management of HAP

umbrella definition of HCAP for this purpose (UPP).

What is the micro-organism profile of HAP/VAP?

Gram-negative bacteria are the most common pathogens causing HAP/VAP in the Indian setting (UPP), and should be routinely considered as the most common etiological agents of HAP/VAP.

What is the approach to diagnosis of HAP/VAP?

1. HAP/VAP can be clinically defined [Figure 2] using modified CDC criteria (2A).
2. In patients with a strong suspicion of VAP/HAP but insufficient evidence for the presence of infection, periodic re-evaluation should be done (2A).
3. In patients with suspected VAP/HAP, one or more lower respiratory tract samples and blood should be sent for cultures prior to institution of antibiotics (1A).
4. All patients suspected of having HAP should be further evaluated with good-quality sputum microbiology (3A).
5. CT scan should not be routinely obtained for diagnosing HAP/VAP (3A).
6. Semi-quantitative cultures can performed in lieu of qualitative cultures (1A).
7. Appropriate management should not be delayed in clinically unstable patients for the purpose of performing diagnostic sampling (UPP).

Are quantitative methods of culture better than semi-quantitative methods?

Semi-quantitative cultures of lower respiratory tract secretions are easier and equally discriminatory for the presence of pneumonia, as compared to quantitative cultures (UPP).

Are invasive techniques to collect lower respiratory tract secretions better than blind endotracheal aspirates?

1. Quantitative and or semi-quantitative cultures using various sampling techniques like ETA, bronchoscopic, or non-bronchoscopic BAL and PSB are equally useful for establishing the diagnosis of HAP/VAP (2A).
2. Semi-quantitative culture on blind (non-bronchoscopic) ETA sample (preferably obtained through a sterile telescoping catheter system) is a reasonable choice (2A).
3. In a patient suspected of having VAP, the preferred method for lower respiratory tract sample collection (blind or targeted, bronchoscopic or non-bronchoscopic) depends upon individual preferences, local expertise, and cost; however, blind ETA sampling is the easiest and equally useful (UPP).

What is the role of biomarkers in the diagnosis of HAP/VAP?

1. Currently available biomarkers should not be used to diagnose HAP/VAP (1A).
2. Where available, serum procalcitonin levels <0.5 ng/mL may help in differentiating bacterial HAP/VAP form other non-infective etiologies, and may help in decisions for antibiotic cessation (2B).

Is combined clinico-bacteriological strategy better than either strategy used alone?

Both clinical and bacteriological strategies can be combined to better diagnose and manage HAP and VAP (UPP).

How do we decide on the empiric antibiotic regimen to be started in a case of suspected HAP/VAP?

1. Every ICU/hospital should have its own antibiotic policy for initiating empiric antibiotic therapy in HAP based on their local microbiological flora and resistance profiles (1A). This policy should be reviewed periodically.
2. In hospitals that do not have their own antibiotic policy, the policy given in these guidelines is recommended (3A). However, they should strive toward formulating their own antibiotic policy.

What is the role of routine endotracheal aspirate culture surveillance?

Routine endotracheal aspirate culture is not recommended. An antibiogram approach should be followed wherever feasible (2A).

Is there a benefit of combination therapy over monotherapy for the treatment of HAP/VAP and HCAP?

Although there is no evidence to suggest that combination therapy is superior to monotherapy, the expert group recommended initial empiric therapy as a combination due to the high prevalence rates of MDR pathogens in late-onset

HAP/VAP [Table 16] and with an aim to ensure the chances of appropriateness of the initial regimen (UPP). However, once the culture reports are available, the regimen should be de-escalated to the appropriate monotherapy (1A).

What is the recommended strategy for initiating antibiotics in suspected HAP/VAP?

1. In patients with suspected HAP, antibiotics should be initiated as early as possible after sending the relevant samples for culture (1A).
2. The exact choice of antibiotic to be started is based on local availability, antibiotic resistance patterns, preferred routes of delivery, other complicating factors, and cost.
3. The initial combination therapy should be converted to appropriate monotherapy once the culture reports are available (1A).
4. Colistin is not recommended as an initial empiric therapy for HAP/VAP (3A).
5. Combination therapy with colistin and meropenem is not recommended (2A).

Is antibiotic de-escalation useful? What is the strategy for antibiotic de-escalation?

1. The strategy for de-escalation of antibiotics is strongly recommended (1A). However, as the de-escalation strategy entirely rests on microbiology, appropriate microbiological samples should be sent before initiation of antibiotics [Figure 2].
2. Among patients with suspected VAP in whom an alternate cause for pulmonary infiltrates is identified, it is recommended that antibiotics should be stopped (1A).
3. If cultures are sent after initiation of antibiotics, and there is clinical improvement with subsequent cultures being sterile, antibiotics should be continued for 7 days followed by assessment of CPIS on the 7th day. If CPIS is <6, antibiotics can be stopped, while if it is ≥6, treatment should be continued for 10–14 days.
4. If cultures sent before starting antibiotics are negative and there is clinical worsening, it is recommended that a review of the current management plan including the choice of antibiotics be performed. Microbiological workup should be repeated including performance of fungal cultures. One also needs to look for alternate sources of sepsis (especially one or more foci of undrained infection), and consider non-infective causes.
5. Empiric antifungal therapy (on day 3) should not be used as a routine in all patients if cultures are sterile and there is clinical worsening (3A).

What is the optimal duration of antibiotic therapy?

1. In patients with VAP due to *Pseudomonas*, *Acinetobacter*, and MRSA, a longer duration (14 days) of antibiotic course is recommended (1A). Assessment of CPIS on day 7 may identify the patients in whom therapy could be stopped early (2A).
2. In other patients with VAP who are clinically improving, a 7-day course of antibiotics is recommended (1A).

Is continuous infusion of antibiotics better than intermittent doses?

Antibiotic administration in critically ill patients according to their pharmacokinetic/pharmacodynamic profile [Table 17] is recommended as it is associated with superior clinical outcomes (2A).

What is the role of inhaled antibiotics in the treatment of VAP?

1. Aerosolized antibiotics (colistin and tobramycin) may be a useful adjunct to intravenous antibiotics in the treatment of MDR pathogens where toxicity is a concern (2A).
2. Aerosolized antibiotics should not be used as monotherapy and should be used concomitantly with intravenous antibiotics (2A).

Should one treat ventilator-associated tracheobronchitis?

Patients with proven VAT should not be treated with antibiotics (2A).

What are the drugs of choice for treatment of methicillin-resistant Staphylococcus aureus?

1. In patients with suspected MRSA infection, we recommend the use of empiric vancomycin (1A) or teicoplanin (2A). The use of linezolid in India should be reserved because of its potential use in extensively drug-resistant TB.
2. Linezolid is an effective alternative to vancomycin (1A) if the patient (a) is vancomycin intolerant, (b) has renal failure, and (c) is harboring vancomycin-resistant organism.

How to treat MDR Acinetobacter infections?

1. For treatment of MDR *Acinetobacter* infections, we recommend the following drugs: carbapenems (1A), colistin (1A), sulbactam plus colistin (2B), sulbactam plus carbapenem (2B), and polymyxin B (2A).
2. Combination therapy with sulbactam and colistin or carbapenem for MDR *Acinetobacter* (in proven cases or suspected cases with multi-organ dysfunction syndrome) may be initiated. Sulbactam should be stopped after 5 days in patients responding to treatment (2B).

How to treat MDR Pseudomonas infections?

For treatment of MDR *Pseudomonas*, we recommend initial combination chemotherapy with a carbapenem and either a fluoroquinolone or an aminoglycoside (1A). Treatment should then be de-escalated to appropriate monotherapy.

What are the other good practices to be followed in the ICU?

1. Stress ulcer prophylaxis: Sucralfate should be used in patients with HAP, while H-2 receptor antagonists or proton pump inhibitors should be used in patients with VAP.

2. Early enteral feeding: Enteral feeding is superior to parenteral nutrition and should be used whenever tolerated and in those without any contraindications to enteral feeding.
3. DVT prophylaxis: DVT prophylaxis with unfractionated heparin (5000 U thrice a day) or a low-molecular-weight heparin should be routinely used in all ICU patients with no contraindications to prophylactic anticoagulation.
4. Glucose control: A plasma glucose target of 140–180 mg/dL is recommended in most patients with HAP/VAP, rather than a more stringent target (80–110 mg/dL) or a more liberal target (180–200 mg/dL).
5. Blood products: Red cells should be transfused at a hemoglobin threshold of <7 g/dL except in those with myocardial ischemia and pregnancy. Platelet transfusion is indicated in patients with platelet count <10,000/μL, or <20,000/μL if there is active bleeding. Fresh frozen plasma is indicated only if there is a documented abnormality in the coagulation tests and there is active bleeding or if a procedure is planned.

INTRODUCTION

Pneumonia is an important clinical condition which is commonly confronted both by a pulmonologist as well as a general practitioner. In spite of plethora of information on the subject, one often finds it difficult to make critical decisions. There are several evidence-based guidelines to guide treatment decisions. However, there are no Indian guidelines, which consider the differences in healthcare organization, prescription habits of doctors, drug availability, and costs. Moreover, the clinical practice is different at different levels of healthcare in the country. It was therefore, considered important to frame evidence-based, consensus guidelines for the use of physicians.

METHODOLOGY

The process of pneumonia guidelines development was undertaken as a joint exercise by the Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, with sponsorship from two National Pulmonary Associations (Indian Chest Society and National College of Chest Physicians). The committee constituted for this purpose included representation of the two associations, and experts from other institutes and medical colleges including those from the Departments of Internal Medicine, Microbiology, Pharmacology, and Radiodiagnosis.

The methodology comprised desk-review followed by a joint workshop. The review of literature was performed by searching the electronic sources (PubMed, EmBase) using the free-text terms: pneumonia, CAP, VAP, HCAP, HAP. A total of 500 articles were reviewed in detail. All major international guidelines available from the Infectious Disease Society of America (IDSA), American Thoracic Society (ATS), British Thoracic Society (BTS), and European Respiratory Society (ERS) were also reviewed.

The search was conducted under four subgroups [A. Diagnosis of community-acquired pneumonia (CAP); B. Management of CAP; C. Diagnosis of hospital-acquired, healthcare-associated, and ventilator-associated pneumonia (HAP, HCAP, and VAP, respectively); D. Management of HAP, HCAP, and VAP], each with a Group Chair and a Rapporteur. Important questions were framed on the basis of discussions on issues with reference to the Indian context. The available evidence as well as the questions were circulated to all the group members before the joint workshop. Discussions for grading of evidence and recommendations were held in four different groups and thereafter together in the joint meeting of all the groups. Final decisions in the joint group were based on a consensus approach on the majority voting.

Table 1: Classification of level of evidence and grading of recommendation based on the quality of evidence supporting the recommendation

Classification of level of evidence	
Level 1	High-quality evidence backed by consistent results from well-performed randomized controlled trials, or overwhelming evidence from well-executed observational studies with strong effects
Level 2	Moderate-quality evidence from randomized trials (that suffer from flaws in conduct, inconsistency, indirectness, imprecise estimates, reporting bias, or other limitations)
Level 3	Low-quality evidence from observational evidence or from controlled trials with several serious limitations
Useful Practice Point	Not backed by sufficient evidence; however, a consensus reached by working group, based on clinical experience and expertise
Grading of recommendation based on the quality of evidence	
Grade A	Strong recommendation to do (or not to do) where the benefits clearly outweigh the risk (or vice versa) for most, if not all patients
Grade B	Weaker recommendation where benefits and risk are more closely balanced or are more certain

The modified grade system was used for classifying the quality of evidence as 1, 2, 3 or usual practice point (UPP) [Table 1].[1] The strength of recommendation was graded as A or B depending upon the level of evidence [Table 1]. Grade A recommendations in the guidelines should be interpreted as recommended and the grade B recommendations as suggested. While making a recommendation, the issues of practicality, costs, and feasibility in the country at different levels of healthcare was also taken into consideration.[2]

The final document was reviewed by the committee members as well as by other external experts.

COMMUNITY-ACQUIRED PNEUMONIA

Definitions

What is the definition of CAP?

CAP can be defined both on clinical and radiographic findings. In the absence of chest radiograph, CAP is defined as: (a) symptoms of an acute lower respiratory tract illness (cough with or without expectoration, shortness of breath, pleuritic chest pain) for less than 1 week; and (b) at least one systemic feature (temperature >37.7°C, chills, and rigors, and/or severe malaise); and (c) new focal chest signs on examination (bronchial breath sounds and/or crackles); with (d) no other explanation for the illness (adapted from Ref [3])

When a chest radiograph is available, CAP is defined as: symptoms and signs as above with new radiographic shadowing for which there is no other explanation (not due to pulmonary edema or infarction).[3] Radiographic shadowing may be seen in the form of a lobar or patchy consolidation, loss of a normal diaphragmatic, cardiac or mediastinal silhouette, interstitial infiltrates, or bilateral perihilar opacities, with no other obvious cause.

Epidemiology and Etiology

What is the epidemiology of CAP in the world?

According to the CDC estimates, 1.1 million people in the US were hospitalized with pneumonia and more than 50,000 people died from the disease in 2009.[4] The epidemiological data from various countries are summarized in Table 2.[5-15]

What is the epidemiology of CAP in India?

There are no large studies from India on the incidence of CAP, but mortality data on the total number of deaths caused by "lower respiratory tract infections" are available.[16] The number of deaths due to lower respiratory tract infections was 35.1/100,000 population in the year 2008 [Table 3] compared to 35.8/100,000 population for TB, while it was 194.9/100,000 for infectious and parasitic diseases. Thus, around 20% of the mortality due to infectious diseases in India is caused by lower respiratory tract infections. The reported mortality of CAP from India is similar to that reported elsewhere in the world. In one report of 150 patients admitted with CAP, 12 (8%) patients died in-hospital, while 4 (2.7%) succumbed within 30 days after discharge.[17] In another study on 72 consecutive patients with CAP over 18 months, 35% of elderly and 14% of young patients succumbed to fulminant sepsis or respiratory failure.[18] The mortality has been variably reported between 3.3% and 11% in other studies from India.[17,19,20]

What is the etiology of CAP worldwide?

A microbiological diagnosis could be made in only 40–71% of cases of CAP [Table 4]. *Streptococcus pneumoniae* is the most common etiological agent, but the proportion in different studies is variable [Table 4].[5,11,21-28] Viruses are responsible for CAP in as much as 10–36% of the cases. The widespread antibiotic (mis)use is probably responsible for decreasing culture rates in CAP. In 2009, Medicare data from 17,435 patients hospitalized for CAP showed that an etiological agent was identified in 7.6% as opposed to >90% in the pre-penicillin era.[29]

Table 2: Summary of studies on epidemiology of CAP from across the globe

Reference	Year	Country	No.	Findings
Donalisio *et al.*[5]	2011	Brazil	66	Prospectively studied 66 patients (>14 years of age) with CAP. The mortality rate was 4.9%
Bruns *et al.*[6]	2011	The Netherlands	356	In patients who had recovered from CAP, cumulative 1-year, 5-year, and 7-year mortality rates were 17%, 43%, and 53%, respectively, as compared with 4%, 19%, and 24% for an age-matched and sex-matched population reference cohort
Ruhnke *et al.*[7]	2010	USA	569,524	Study of CAP admissions between 1993 and 2005. Age/gender-adjusted mortality at discharge decreased from 8.9% to 4.1% from 1993 to 2005
Capelastegui *et al.*[8]	2010	Spain	960	418 hospitalized and 542 ambulatory patients with CAP identified. The hospitalization rate was 43.5% and the global 30-day mortality was 4%. The incidence of pneumonia was 3.1/1000 adults per year
Welte *et al.*[9]	2009	Germany	7508	Mortality rates were low (<2%) in CAP patients treated as outpatients, but were higher (5–20%) among patients hospitalized for CAP and were the highest (up to 50%) in patients admitted to the intensive care unit (CAPNETZ figures)
Vila-Corcoles *et al.*[10]	2009	Spain	11,241	Community-dwelling individuals aged 65 years or more, followed between 2002 and 2005. Incidence rate of overall CAP was 14 cases/1000 person years (10.5 and 3.5, respectively, for hospitalized and outpatient cases). Overall 30-day case-fatality rate was 12.7% (2% in outpatient and 15% in hospitalized patients)
Charles *et al.*[11]	2008	Australia	885	Prospective, multicenter study. The 30-day mortality rate was 5.6%
Viegi *et al.*[12]	2006	Italy	699	287 family practitioners recorded suspected or ascertained CAP cases for 1 year. CAP incidence rates per 1000 population were: 1.69 in men vs. 1.71 in women. Rates of hospitalization and of mortality were 31.8% and 6.0%, respectively
Marrie *et al.*[13]	2005	Canada	8144	Patients aged ≥17 years presenting to seven emergency departments over a 2-year period with CAP were studied. The admission rates were 271/100,000 and 296/100,000 persons, respectively, for years 1 and 2 of the study
Loh *et al.*[14]	2004	Malaysia	108	Prospective study of adult patients. Thirteen patients (12%) died in hospital and 95 (88%) survived to hospital discharge
Fine *et al.*[15]	1996	US	33,148	The overall mortality was 13.7%, ranging from 5.1% for the 2097 hospitalized and ambulatory patients to 36.5% for the 788 ICU patients

CAPNETZ, German Competence Network for Community-acquired pneumonia

Table 3: WHO mortality figures for lower respiratory tract infections in India

Age group (years)	No. of deaths per lakh population in 2008
15–59	6.2
>60	622.2
Overall	35.1

Adapted from reference[16]

What is the etiology of CAP in India?

There are very few Indian reports on the etiological agents of CAP. In a study of blood cultures performed in CAP, *Str. pneumoniae* (35.3%) was the most common isolate, followed by *Staphylococcus aureus* (23.5%), *Klebsiella pneumoniae* (20.5%), and *Haemophilus influenzae* (8.8%).[20] An earlier study also found *Str. pneumoniae* to be the most common cause (35.8%), but it also reported *Mycoplasma pneumoniae* in 15% of the microbiologically positive cases.[19] *Legionella pneumophila* is an important cause which is often not considered in the Indian setting. In a recent study, 27% of patients with CAP were serologically positive for this organism and around 18% demonstrated *L. pneumophila* antigenuria.[30] *Mycoplasma* was found to be the etiological agent in 35% of cases.[18] There are no large studies that have specifically addressed viruses as the cause of CAP apart from pandemic influenza H1N1 virus.

Is the etiology different in different population groups?

Elderly

Str. pneumoniae is the single most common organism identified in hospitalized elderly patients with CAP, accounting for 19–58% of cases.[31-33] *H. influenzae* was also frequently isolated (5–14%).[32-34] In most cases, the microbiological patterns observed in the elderly do not differ significantly from those of the younger populations.[33]

Chronic obstructive pulmonary disease (COPD)

COPD is a common comorbid condition in patients with CAP. It was the most common underlying comorbid condition among 40 cases (57%) in one study[19] and the second most common predisposing factor in another.[35] The spectrum of responsible microorganisms is largely similar to patients without COPD,[36,37] although the incidence of *Pseudomonas aeruginosa* and other Gram-negative bacilli may be increased in COPD.[38] COPD does not appear to increase the mortality of CAP.[39]

Alcoholism

Alcohol consumption increases the relative risk for CAP with a dose–response relationship.[40] *Str. pneumoniae* is found more frequently in patients with alcohol abuse.[34,41] The odds of bacteremic CAP are higher in these patients.[34] CAP was also more severe in alcoholics, but mortality is not different.[41] In contrast to the popular belief, no strong evidence was found to suggest increased prevalence of *Klebsiella* in alcohol users.

Diabetes mellitus

The etiological agents, the bacteremia or empyema rates are not different in diabetics compared to the non-diabetic population.[42] However, diabetes was significantly associated with higher mortality. Diabetes was also found to be more frequent in patients with bacteremic pneumococcal pneumonia compared to those with either non-bacteremic pneumococcal pneumonia or CAP of other etiologies.[43] Recent studies also suggest that pre-existing diabetes is associated with a higher mortality following CAP.[44,45] The proposed mechanism is due to worsening of pre-existing cardiovascular and kidney disease and not due to an altered immune response.[45] Diabetes is a frequently reported co-morbid condition in Indian reports.[17,19,35]

Risk factors for *Pseudomonas* pneumonia

Immunocompromised states, chronic respiratory disease, enteral tube feeding, cerebrovascular disease, and other chronic neurological disorders have all been found to be predictors of CAP due to *P. aeruginosa*.[46] In one study, the presence of a pulmonary comorbidity (which included chronic bronchitis, COPD, asthma, bronchiectasis, or others) was the strongest predictor of *P. aeruginosa* pneumonia.[47]

Diagnosis

What are the clinical features of CAP and what is their usefulness in diagnosis?

Common symptoms of CAP include fever, cough, sputum production, dyspnea, and pleuritic chest pain. Physical examination may reveal focal areas of bronchial breathing and crackles. The frequency of each symptom is quite variable [Table 5].[19,24,30,35,49,52-54] Bronchial breathing, despite being an important physical sign, does not find mention in most of these studies. Utility of the clinical signs either alone or in combination is debatable, and they are often found to lack sensitivity for the diagnosis of CAP.[52] Temperature >100.4°F, heart rate >110 beats/min, and pulse oximetric saturation <96% have been found to be strong predictors of CAP.[53] However, no single characteristic is adequately sensitive and specific to accurately discriminate CAP from viral illness.[49] Also, respiratory and non-respiratory symptoms associated with a pneumonic illness are less commonly reported by older patients with pneumonia.[54] Certain specific clinical syndromes may be associated with some atypical pathogens like *Mycoplasma* and *Legionella*.

What is the role of chest radiograph in the diagnosis of CAP?

A chest radiograph is the cornerstone for the diagnosis of CAP. In a study of 250 ambulatory patients with febrile respiratory tract infections, physicians' judgment of pneumonia had a sensitivity of 74% (49–90%), specificity of 84% (78–88%), negative predictive value of 97% (94–99%), and a positive predictive value of 27% (16–42%) compared to the chest radiograph.[55] In low-risk patients with a reliable follow-up, chest radiographs are unnecessary for the diagnosis of CAP in the presence of normal vital signs and physical examination findings.[56] A diagnosis of CAP can be suspected if at least one of the

Table 4: Summary of studies reporting the etiology of CAP from various countries

Authors	Year	No.	Type of study	Percentage with microbiological diagnosis (%)	*Str. pneumoniae*	*Sta. aureus*	*Legionella* spp.	*H. influenza*	*M. pneumoniae*	*Chlamydia* spp.	*Pseudomonas* spp.	Other bacteria	Viruses
Donalisio *et al.*[5]	2011	66	Prospective	51	51					8			
Shibli *et al.*[21]	2010	126	Prospective	67	18				18	21			36
Koksal *et al.*[22]	2010	218	Cross-sectional	63	15				14				10
Johansson *et al.*[23]	2010	184	Prospective	67	38	2	1	5	8			8	29
Charles *et al.*[11]	2008	885	Prospective	46	14	1	3	5	9	2	2	2	15
Diaz *et al.*[24]	2007	176	Prospective	55	50		4		4	3			32
Huang *et al.*[25]	2006	389	Prospective	40	3	2	1	21	11	4		6	
Al-Ali *et al.*[26]	2006	35	Prospective	71	26		6	17	9	23		26	
Marrie *et al.*[27]	2005	507	Prospective	48	6			5	15	12			
Lauderdale *et al.*[28]	2005	168	Prospective	59	40			8	24	12		8	11
Summary				40–71%	3–51	1–2	1–6	5–21	4–24	2–23	2	2–26	10–36

Table 5: Summary of studies analyzing the frequency of symptoms of CAP

Authors	Year	No.	Cough	Purulent expectoration	Fever	Dyspnea	Chest pain	Crackles	BBS
Javed *et al.*[30]	2010	113	88		83	64		37	9
Shah *et al.*[35]	2010	100	99	65	95		75		
Diaz *et al.*[24]	2007	176	81	67		71	23		
Bruns *et al.*[48]	2007	288	63			86	31	52	
Muller *et al.*[49]	2007	545	91	72	53	72		72	
Bansal *et al.*[19]	2004	70	97	87	90	48	34	98	47
Riquelme *et al.*[50]	1997	100	67	52	64	71	34	65	2
Sow *et al.*[51]	1996	217		36	68	27	96	70	
Summary			63–99	36–87	53–95	27–72	23–96	52–98	2–47

BBS, bronchial breath sound

following findings is present on the chest radiograph: (i) an asymmetric increase in lung opacification with air bronchogram; (ii) presence of silhouette sign; (iii) an area of increased opacity bounded by a well-defined interface against adjacent aerated lung (such as along a fissure); (iv) if only an anterior–posterior view is obtained (such as a portable examination), increased attenuation of the cardiac shadow; and (v) for radiographs with widespread airspace disease, more asymmetric or multifocal distribution of opacification.[57] There is fair to good inter-observer reliability between radiologists in identifying the presence of infiltrate, multilobar disease, and pleural effusion.[58] A chest radiograph is also helpful in differentiating CAP from other causes of acute respiratory symptoms like pulmonary edema, pulmonary infarction, pleural effusion, or tuberculosis.

Importantly, resolution of chest radiograph findings may lag behind clinical cure during follow-up, and up to 50% of patients may not show complete radiographic resolution at 4 weeks.[48] Radiographic resolution may be delayed in the elderly.[59] Patients with radiologic deterioration would almost always have one or the other clinical feature suggestive of clinical failure (persistent fever, abnormal auscultatory findings, or persistent tachypnea).[60] In the presence of such clinical indicators, it becomes essential to obtain a chest radiograph. Lack of partial radiographic resolution by 6 weeks, even in asymptomatic patients, would require consideration of alternative causes (e.g. endobronchial obstruction or non-infectious causes like pulmonary vasculitis, organizing pneumonia, and others).[61]

Recommendations:

1. Wherever feasible, a chest radiograph should be obtained in all patients suspected of having CAP (1A).
2. In the absence of availability of chest radiograph, patients may be treated on the basis of clinical suspicion (3A).
3. Chest radiograph should be repeated if the patient is not improving and also for all those patients who have persistence or worsening of symptoms/physical signs or those in whom an underlying malignancy needs to be excluded. It is not routinely necessary to repeat a chest radiograph in patients who have improved clinically (2A).

What is the role of computed tomography (CT) in the diagnosis of CAP?

High-resolution CT (HRCT) findings of CAP include air space consolidation, ground-glass attenuation, and thickening of the bronchovascular bundle.[62] In a retrospective study of 75 patients with pneumococcal pneumonia, consolidation (84%) was the most frequently observed finding followed by ground-glass opacity (82.7%), bronchial wall thickening (61.3%), and centrilobular nodules (49.3%). Airway dilatation (21.6%), pleural effusion (33.3%), lymphadenopathy (34.8%), and pulmonary emphysema (21.3%) were also observed.[63] Centrilobular nodules favored non-bacterial pneumonia, while airspace nodules were more common with bacterial pneumonia (specificities of 89% and 94%, respectively) when located in the outer lung areas.[64] When centrilobular nodules were the principal finding, they were specific but lacked sensitivity for non-bacterial pneumonia (specificity 98% and sensitivity 23%). CT could discriminate bacterial pneumonia from non-bacterial pneumonia with a sensitivity and specificity of 70% and 84%, respectively. Thus, HRCT findings are not sufficient for tailoring antibiotic treatment. A CT chest may, however, be useful in the diagnosis of complications of pneumonia like lung abscess and empyema. In up to 27% of cases, pneumonia might be demonstrated on CT with a negative or non-diagnostic chest radiograph.[65] However, studies that have investigated clinical interventions and treatment decisions based on HRCT findings compared to chest radiography are lacking. Therefore, the clinical utility of a CT chest in patients with suspected CAP and a negative chest radiograph remains unclear. Besides, CT scanning is an expensive, resource-intensive diagnostic modality with limited availability, and entails the risk of high radiation exposure.

Recommendations:

1. CT of the thorax should not be performed routinely in patients with CAP (2A).
2. CT of the chest should be performed in those with non-resolving pneumonia and for the assessment of complications of CAP (2A).

Which microbiological investigations need to be performed in CAP?

Blood cultures

Blood cultures have a low sensitivity but high specificity in identifying the microbial etiology. The yield of blood cultures ranged between 5% and 33% in various small studies.[66-72] In a large study of 25,805 Medicare patients, bacteremia was detected in 7% of patients and 5% of all patients had at least one contaminated blood culture.[73] In a systematic review, blood cultures were true-positive in 0–14% of cases.[74] They led to antibiotic narrowing in 0–3% and change in antibiotic because of a resistant organism in 0–1% of patients. Despite the low yield of blood culture, the microbial etiology of CAP is identified in a significant proportion of patients with this investigation.

Recommendations:

1. Blood cultures should be obtained in all hospitalized patients with CAP (2A).
2. Blood cultures are not required in routine outpatient management of CAP (2A).

Sputum Gram stain and cultures

The yield of sputum cultures varies from 34 to 86%.[75,76] In a meta-analysis of 12 studies, the sensitivity and specificity of sputum Gram stain was 15–100% and 11–100%, respectively, in the diagnosis of pneumococcal CAP, compared to sputum culture.[77] Despite a low sensitivity, Gram stain of sputum is useful as it provides rapid results and can help narrow down the etiology. Twenty to 40 fields from sputum smear should be examined microscopically under low power. The number of epithelial cells in representative fields that contain cells should be averaged. If epithelial cells are >10/ low power field, the sample should be rejected for culture. If the number of pus cells is 10 times the number of epithelial cells with 3+ to 4+ of a single morphotype of bacteria, the specimen should be accepted for culture.[78]

[Refer to the section on hospital-acquired pneumonia for discussion of various invasive techniques for the collection of respiratory specimens]

Recommendations:

1. An initial sputum Gram stain and culture (or an invasive respiratory sample as appropriate) should be obtained in all hospitalized patients with CAP (2A).
2. Sputum quality should be ensured for interpreting Gram stain results (2A).
3. Sputum for acid-fast bacilli (AFB) should be obtained as per RNTCP guidelines for non-responders (UPP).

Pneumococcal antigen detection

Pneumococcal antigen can be detected in the urine using proprietary rapid immunochromatographic membrane tests. The sensitivity ranges from 65 to 80% compared to gold standard (Gram stain of sputum or cultures of sputum and blood).[79-81] As all empiric treatment regimens are designed to cover *Str. pneumoniae*, the test only confirms a pneumococcal etiology without any significant change in the treatment protocol. Considering the cost and availability of the test, it may not have a favorable cost–benefit ratio.

Recommendation:

Pneumococcal antigen detection test is not required routinely for the management of CAP (2A).

Pneumococcal PCR

Pneumococcal PCR has a poor sensitivity. In a recent meta-analysis (22 studies), the summary sensitivity and specificity for pneumococcal PCR (pneumococcal bacteremia as case and healthy people or patients with bacteremia caused by other bacteria as controls) in blood was 57.1% (95% CI, 45.7–67.8%) and 98.6% (95% CI, 96.4–99.5%), respectively.[82]

Recommendation:

Pneumococcal PCR is not recommended as a routine diagnostic test in patients with CAP (1A).

Legionella antigen detection

The pooled sensitivity and specificity of various assays for *Legionella* urinary antigen detection is 0.74 (95% CI, 0.68–0.81) and 0.991 (95% CI, 0.98–0.997), respectively.[83] In one study, the treatment was altered in more than half the patients from results of the *Legionella* urinary antigen test.[84] *Legionella* is an important causative agent of CAP in India. As the sensitivity is relatively low, a negative test does not rule out the possibility of *Legionella* pneumonia. A positive test is highly specific and potentially changes the duration of antibiotic therapy.

Recommendation:

Legionella urinary antigen test is desirable in patients with severe CAP (1B).

Other atypical pathogens

Mycoplasma, *Chlamydia*, and respiratory viruses are important etiological agents of pneumonia. However, culture techniques for *Mycoplasma pneumoniae* are not only insensitive but also time consuming (2–5 weeks).[85] Serological assays, especially the complement fixation test, are widely used. The sensitivity of these assays varies depending on the timing of collection of the serum sample and the availability of paired serum samples (collected at an interval of 2–3 weeks). IgM assays are more sensitive, but IgM response may be absent in adults.[86] PCR based tests done in respiratory samples are rapid, but a recent review found sensitivity of only 62% compared to serological methods.[87] *Chlamydophila pneumoniae* is very difficult to grow in the laboratory, and the usefulness of serology for the diagnosis of acute infections by *C. pneumoniae* is doubtful.[88] The micro-immunofluorescence test is currently considered the gold standard for the serodiagnosis of *C. pneumoniae* infection. There is, however, a high rate of false-positive and false-negative test results, attributed to delayed and unpredictable development of IgM and IgG, and lack of standardized methods.[89] Molecular diagnostic techniques like PCR are not widely available and not appropriately validated. If *Legionella*, *M. pneumoniae*, and *C. pneumoniae* are considered, only *Legionella* spp. are associated with significant mortality.[90] Due to empiric coverage and a widely favorable outcome for atypical agents, testing for *Mycoplasma* and *Chlamydia* in patients with mild to moderate CAP might not be required. Besides, there are no well-validated rapid tests for *Mycoplasma* and *Chlamydia*.[29] Although serological and PCR-based tests are available for respiratory viruses, they seldom have any bearing on the management of the patient from influenza. Reverse transcriptase PCR (RT-PCR) is a rapid and accurate method for the detection of influenza virus infection,[91] but is not routinely required except in the setting of an outbreak.

Recommendation:

Investigations for atypical pathogens like *Mycoplasma*, *Chlamydia*, and viruses need not be routinely done (2A).

What general investigations are required in patients with CAP?

General

Apart from a chest radiograph, there are few investigations required for outpatient management. Use of pulse oximetry increases the detection of arterial hypoxemia.[92] Arterial saturation ≤90% has good specificity but low sensitivity for adverse outcomes in CAP, and complements clinical severity scoring.[93] In admitted patients, it is a usual practice to perform plasma glucose, urea, and electrolytes, complete blood count, and liver function tests. Urea also forms a part of CURB-65 score for severity assessment. A delay in oxygenation assessment of >1 h is associated with an increase in time to first antibiotic dose, and a delay in oxygenation assessment of >3 h is associated with an increased risk of death in patients admitted to the intensive care unit (ICU).[94]

Recommendations:

1. For patients managed in an outpatient setting, no investigations are routinely required apart from a chest radiograph (3A).
2. Pulse oximetry is desirable in outpatients (2B).
3. Pulse oximetric saturation, if available, should be obtained as early as possible in admitted patients (2A). Arterial blood gas analysis should be performed in those with an oxygen saturation ≤90% and in those with chronic lung disease (3A).
4. Blood glucose, urea, and electrolytes should be obtained in all hospitalized patients with CAP (3A).
5. Full blood count and liver function tests are also helpful in the management of patients with CAP (3B).

Role of biomarkers

In most instances, the diagnosis of CAP is made with certainty based on clinical features and chest radiograph findings. However, CAP can occasionally be confused with pulmonary edema or pulmonary embolism. Also, it is difficult to differentiate CAP of viral etiology from that of bacterial etiology. Biomarkers like procalcitonin (PCT) and C-reactive protein (CRP) may be of some value in resolving these issues. PCT levels rise in many inflammatory conditions and more so in bacterial infections. PCT can be considered as an adjunct to clinical acumen.[95] Although PCT cannot be used as a sole marker for taking decisions of initiating antibiotics, it can be helpful in differentiating the presence or absence of bacterial CAP.[96-98] As PCT is not a marker of early infection (increases after 6 h), a single value may be falsely low and serial values should be obtained to guide antibiotic use in the course of a suspected infective illness. Certain studies have also shown a role for CRP as a diagnostic marker for CAP.[99,100] CRP levels can independently distinguish pneumonia from exacerbations of asthma, and CRP levels have been used to guide antibiotic therapy and reduce antibiotic overuse in hospitalized patients with acute respiratory illness.[101] On the contrary, a systematic review concluded that additional diagnostic testing with CRP is unlikely to alter management decisions such as antibiotic prescribing or referral to hospital.[102]

Table 6: Summary of commonly used criteria for risk stratification in CAP

CURB-65	CRB-65	SMART-COP	SMRT-CO	ATS-IDSA criteria
Confusion Urea ≥7 mmol/L Respiratory rate ≥30/min Low blood pressure (diastolic blood pressure ≤60 mm Hg or systolic blood pressure ≤90 mm Hg) Age ≥65 years	Confusion Respiratory rate ≥30/min Low blood pressure (diastolic blood pressure ≤60 mm Hg or systolic blood pressure ≤90 mm Hg) Age ≥65 years	Low systolic blood pressure (<90 mm Hg) Multilobar CXR involvement Low albumin (<3.5 g/dL) Respiratory rate (≥25/min) Tachycardia (≥125/min) Confusion Poor oxygenation (PaO2 <70 mm Hg; SpO2 <93%) Low pH (<7.35)	Low systolic blood pressure (<90 mm Hg) Multilobar CXR involvement Respiratory rate (≥25/min) Tachycardia (≥125/min) Confusion Poor oxygenation (PaO2 <70 mm Hg; SpO2 <93%)	Major criteria Invasive mechanical ventilation Septic shock with the need for vasopressors Minor criteria Respiratory rate ≥30 breaths/min PaO_2/FiO_2 ratio ≤250 Multilobar infiltrates Confusion/disorientation Uremia (BUN level ≥20 mg/dL) Leukopenia (WBC count <4000 cells/mm^3) Thrombocytopenia (platelet count <100,000 cells/mm^3) Hypothermia (core temperature <36°C)

Recommendation:
PCT and CRP measurement need not be performed as routine investigations for the diagnosis of CAP (2A).

Risk Stratification

Should patients with CAP be risk stratified?

The risk assessment of patients with CAP is important for a number of reasons. There is a possibility of adverse outcomes if the initial assessment is not rigorous. On the contrary, one can argue that all patients of CAP should be admitted and treated. However, the high costs of admission and risk of hospital-acquired infections preclude routine admission.[103] Hence, there is a need for risk stratification to decide the site of care and future course of management.

What are the various methods of risk stratification?

There are various scores [Table 6] for assessing the risk in a patient with CAP: pneumonia severity index (PSI), CURB-65, CRB-65, SMART-COP, SMRT-CO, A-DROP, and others.

Pneumonia severity index (PSI)

The PSI is a prognostic prediction rule that defines the severity of illness based on predicted risk of mortality at 30 days.[104] It includes 20 prognostic variables to stratify the risk of death due to CAP into five classes. The mortality risk increases with the increase in class, ranging from 0.4% in class I to 31% with class V. The strengths of the PSI include the rigorous methodology used to derive the score, the reproducibility and the generalizability of the score, and the actual change in the treatment decision based on the score.[105] The limitations are its unwieldiness of use, especially in busy emergencies and outpatient departments, overstress on certain variables, and neglect of social and other important medical factors.[104,106,107]

CURB-65

This score was derived from the pooled data of three large studies on CAP carried out in the United Kingdom, New Zealand, and the Netherlands. Based on this, a 6-point score {Confusion, Urea ≥7 mmol/L, Respiratory rate ≥30 breaths/min, low Blood pressure [diastolic blood pressure (DBP) ≤60 mm Hg or systolic blood pressure (SBP) ≤90 mm Hg], age ≥65 years) was derived, which allowed patients to be stratified according to increasing risk of mortality ranging from 0.7% (score 0) to 40% (score 4).[106] A further model based only on clinical features available from a clinical assessment without laboratory results (confusion, respiratory rate, blood pressure, and age; CRB-65 score) was also tested and found to correlate well with the risk of mortality and need for mechanical ventilation.[108] The CURB-65 and CRB-65 stratified mortality is more clinically useful than the systemic inflammatory response syndrome (SIRS) criteria or the standardized early warning score (SEWS).[109] CURB-65 implementation led to a decrease in antibiotic use without affecting mortality, treatment failure, or clinical response.[110] Also, lack of application of the CURB-65 score led to overtreatment of low-risk patients.[111] CURB-65 was, however, found to be less useful in the age group >65 years compared those below 65 years.[112] Hence, CURB-65 can be supplemented with clinical judgment and/or pulse oximetry.[113-117] In a meta-analysis of 397,875 patients, CRB-65 performed well in stratifying the severity of pneumonia and the resultant 30-day mortality in hospital settings, while it appeared to overpredict the probability of 30-day mortality across all strata of predicted risk in community settings.[118] CRB-65 had an acceptable ability to classify mortality risk in the age group >65 years; patients with CRB-65 ≤1 had a relatively small mortality rate, which suggested that they could be managed as outpatients.[119] The CURB-65 and CRB-65 scores are not as extensively validated as the PSI; however, they are recommended by most societies for the initial assessment and risk stratification of CAP.[3,103,120]

SMART-COP

This score was derived from the Australian CAP Study (ACAPS) of 882 episodes of CAP and was further validated in five external databases, totaling 7464 patients. The SMART-COP is a point-based severity score, consisting of low systolic blood pressure (2 points), multilobar chest radiography involvement (1 point), low albumin level (1 point), high respiratory rate (1 point), tachycardia (1 point), confusion (1 point), poor oxygenation (2 points), and low arterial pH (2 points). A SMART-COP score of ≥3 points identified 92% of patients who received invasive respiratory and vasopressor support.[115]

ATS-IDSA criteria

These criteria are helpful in deciding the level of care (ward vs. ICU) once the admission decision has been made. There are two major and nine minor criteria, and the presence of any of the major criteria or at least three of the minor criteria qualifies for an ICU admission [Table 6].[103] An early transfer to the ICU of a severely ill CAP patient is associated with appropriate utilization of resources and decreased mortality.[103] Most studies have validated the use of these criteria for predicting ICU admission;[121-126] however, there are doubts regarding the use of minor criteria alone in predicting risk.[122,126]

Other criteria

These include the A-DROP, REA-ICU index, CAP-PIRO, and others.[44,68,117,127-135] However, these indices are not as extensively validated as the ones discussed previously and need further validation before being accepted.

What should be the optimum method of risk stratification?

There have been multiple studies comparing these indices.[17,115-117,127,131,136-160] A prospective study from India of 150 patients comparing PSI and CURB-65 found both PSI and CURB-65 to possess equal sensitivity in predicting death from CAP while the specificity of CURB-65 was higher than that of PSI. PSI was more sensitive than CURB-65 in predicting ICU admission.[17] One study found PSI to be the best in stratifying low-risk patients with no difference in overall test performance,[152] while another study comparing PSI, CURB-65, CURB, and CRB-65 found that all four scales had good negative predictive values for mortality in populations with a low prevalence of death but were less useful with regard to positive predictive values.[153] Hence, these indices are more useful in screening out low-risk patients. The use of oxygen saturation or partial pressure of oxygen in blood has been found to be an independent predictor of morbidity and mortality in CAP.[115-117]

Recommendations:

1. Patients with community-acquired pneumonia should be risk stratified (1A).
2. Risk stratification should be performed in two steps [Figure 1] based upon the need for hospital admission followed by assessment of the site of admission (non-ICU vs. ICU). Accordingly, patients can be managed as either outpatient or inpatient (ward or ICU) (1A).
3. Initial assessment should be done with CRB-65. If the score is >1, patients should be considered for admission (1A).
4. Clinical judgment should be applied as a decision modifier in all cases (3A).
5. Pulse oximetry can be used to admit hypoxemic patients (2A). Hypoxemia is defined as pulse oximetric saturation ≤92% for age ≤50 years and ≤90% in patients aged >50 years (3A).
6. Patients selected for admission can be triaged to the ward (non-ICU)/ICU based upon the major/minor criteria outlined in Table 6 (2A).
7. If any major criterion or ≥3 minor criteria are fulfilled, patients should generally be admitted to the ICU (1A).

Antibiotic Use

Which are the antibiotics useful for empiric treatment in various settings?

The initial empiric antibiotic treatment is based on a number of factors: (a) the most likely pathogen(s); (b) knowledge of local susceptibility patterns; (c) pharmacokinetics and pharmacodynamics of antibiotics; (d) compliance, safety, and cost of the drugs; and (e) recently administered drugs.

The empiric antibiotic treatment is primarily aimed at *Str. pneumoniae* as it is the most prevalent organism in CAP. The Indian data show a good response of *Str. pneumoniae* to commonly administered antibiotics.[17,161] Various studies have shown results favoring different groups of antibiotics [Table 7].[165-169,171-174,178-184,] The evidence does not support the choice of any particular antibiotic since individual study results do not reveal significant differences in efficacy between various antibiotics and antibiotic groups.[175] The commonly used antibiotics are either β-lactams or macrolides.

Is there a need to cover atypical organisms?

Atypical organisms, especially *Mycoplasma*, *Chlamydia*, and *Legionella*, also contribute significantly to the incidence of CAP. However, the need for empiric treatment of these organisms in mild CAP in the outpatient setting has been challenged as evidence suggests no benefit of covering these organisms with appropriate antibiotics in the outpatient setting.[90,162,163,170,176,177] Combination therapy should be restricted to patients with severe pneumonia.[103,120] Its advantages include expansion of the antimicrobial spectrum to include atypical pathogens and possibly immunomodulation. Combination therapy in patients with severe pneumonia has been shown to decrease mortality.[185-192] Monotherapy suffices for less severe pneumonia treated on outpatient basis. Indications for combination therapy are given in Table 8. Oral macrolides should be used with caution in the elderly as their use has been associated with increased cardiovascular mortality.[193]

What is the role of fluoroquinolones in empiric treatment of CAP in India?

Fluoroquinolones have been recommended in various guidelines for the empiric treatment of CAP.[3,103,120] Although there is significant antimicrobial efficacy of fluoroquinolones,[169,173,180,182,184,194] all studies have been carried out in low prevalence settings of tuberculosis. There is enough evidence to suggest that fluoroquinolone use is associated with masking of tubercular infection and increased risk of drug resistance to *M. tuberculosis* [Table 9].[195-199] Therefore, the indiscriminate empiric use of these drugs for the treatment of CAP in India should be discouraged.

What should be the time to first antibiotic dose?

Intuitively, antibiotics should be started as soon as possible

Table 7: Summary of studies on choice of antibiotics for treatment of CAP

Author(s)	Year	Type of study	Conclusions
Mills *et al.*[162]	2005	Meta-analysis	18 trials totaling 6749 in non-severe all-cause CAP; compared b-lactams vs. atypical cover; clinical outcomes not improved with atypical cover
Shefet *et al.*[163]	2005	Cochrane meta-analysis	24 trials including 5015 randomized patients; no benefit of atypical cover (fluoroquinolone monotherapy vs. non-atypical monotherapy)
Metersky *et al.*[164]	2007	Retrospective analysis	2209 patients with bacteremic pneumonia; initial antibiotic treatment including a macrolide agent was associated with improved outcomes
Reyes Calzada *et al.*[165]	2007	Prospective multicenter study	425 hospitalized patients; b-lactam monotherapy associated with increased risk of readmission
Iannini *et al.*[166]	2007	Retrospective, multicenter study	87 of 122 patients showed low-level erythromycin resistance
Tamm *et al.*[167]	2007	Prospective, randomized, multicenter study	Compared ceftriaxone plus either azithromycin or clarithromycin or erythromycin for moderate–severe CAP; equivalence noted
Dartois *et al.*[168]	2008	Randomized, double-blind, phase 3 multinational trial	Compared tigecycline with levofloxacin for CAP PSI 2–4; tigecycline was safe and of similar efficacy to levofloxacin
Lloyd *et al.*[169]	2008	Randomized control trial	Compared moxifloxacin vs. levofloxacin + ceftriaxone in 738 patients requiring hospitalization; no difference in efficacy; moxifloxacin cheaper
Maipmon *et al.*[170]	2008	Meta-analysis	No advantage of atypical coverage in mild–moderate outpatient CAP
Paris *et al.*[171]	2008	Randomized, open-label, non-inferiority study	Compared azithromycin 1g OD ´ 3 days to amoxicillin–clavulanic acid 875/125 mg BD ´ 7 days; no difference in safety and efficacy
Pertel *et al.*[172]	2008	Two phase-3 randomized, double-blind trials	Daptomycin was not effective for the treatment of CAP, including infections caused by *Streptococcus pneumoniae* and *Staphylococcus aureus*
Ye *et al.*[173]	2008	Retrospective analysis of claims data	2968 patients treated with levofloxacin and 4558 with a macrolide; rates of treatment failure less with levofloxacin; overall CAP-related hospitalizations and costs did not differ significantly
Bergallo *et al.*[174]	2009	Double-blind, randomized, phase 3 comparison study	Tigecycline was safe, effective, and non-inferior to levofloxacin in hospitalized patients with CAP
Bjerre *et al.*[175]	2009	Cochrane meta-analysis	Six RCTs assessing five antibiotic pairs with 1857 patients; evidence insufficient to make evidence-based recommendations for the choice of antibiotic; individual study results do not reveal significant differences in efficacy between various antibiotics and antibiotic groups
Liu *et al.*[176]	2009	Prospective study	610 patients; nonsusceptibility of *Str. pneumoniae* to penicillin and azithromycin was 22.2% and 79.4%, respectively
Lui *et al.*[177]	2009	Prospective, observational study	1193 patients; 28% of CAP caused by atypical organisms; disease severities and outcomes similar to those of patients with CAP due to other organisms
Tanaseanu *et al.*[178]	2009	Prospective, double-blind, non-inferiority phase 3 RCT	IV tigecycline was non-inferior to IV levofloxacin and was well tolerated
Tessmer *et al.*[179]	2009	Observational study of German competence network CAPNETZ	1854 patients; compared b-lactam (BL) monotherapy to b-lactam/macrolide (BLM) combination; BLM therapy with CRB-65 risk classes of 2 or higher was superior in respect to 14-day mortality and was also associated with lower risk of treatment failure
von Baum *et al.*[90]	2009	Prospective analyses from CAPNETZ	307 of 4532 patients had *Mycoplasma pneumoniae*; relatively benign presentation; atypical coverage needs to be reconsidered
An *et al.*[180]	2009	Meta-analysis	Seven RCTs involving 3903 patients; moxifloxacin monotherapy was associated with similar clinical treatment success rates and similar mortality to b-lactams
File *et al.*[181]	2010	Two randomized, double-blind, multicenter trials	614 patients each in ceftaroline and ceftriaxone groups for PSI 3–4 (non-ICU); ceftaroline was non-inferior to ceftriaxone in the individual trials, while clinical cure rates were numerically higher in integrated analysis
Hess *et al.*[182]	2010	Retrospective cohort study	3994 patients; treatment failure less likely with quinolones than with azithromycin, an effect particularly marked in high-risk patients
Cai *et al.*[183]	2011	Meta-analysis	Eight RCTs involving 4651 patients; compared with empiric antibiotic regimens, tigecycline monotherapy was associated with similar clinical treatment success rates, higher adverse effects, and similar all-cause and drug-related mortality
Ewig *et al.*[184]	2011	Retrospective cohort study	4091 patients; 2068 patients received moxifloxacin and 1703 lactam monotherapy; moxifloxacin monotherapy had higher survival as compared to lactam monotherapy in CRB-65 = 1 or 2

after the diagnosis of CAP is established. In severe CAP, antibiotics should be administered as soon as possible, preferably within 1 hour.[200] In non-severe CAP, a diagnosis should be established before starting antibiotics.[201-205]

Recommendations:

1. Antibiotics should be administered as early as possible; timing is more important in severe CAP (2A).

Outpatient setting

2. Therapy should be targeted toward coverage of the most common organism, namely *Str. pneumoniae* (1A).
3. Outpatients should be stratified as those with or without comorbidities (3A).
4. Recommended antibiotics [Table 10] are oral macrolides (e.g. azithromycin and others) or oral β-lactams (e.g. amoxicillin 500–1000 mg thrice daily) for

Table 8: Indications for empiric combination therapy in CAP

Presence of comorbid medical conditions
Chronic heart, lung, liver, or renal disease
Diabetes mellitus
Alcoholism
Malignancies
Use of antimicrobials within the previous 3 months
Severe CAP with or without comorbidities

Adapted from reference[103]

Table 9: Summary of studies on the use of fluoroquinolones (FQs) in CAP

Author(s)	Year	Type of study	Conclusions
Long *et al.*[195]	2009	Case control study, 428 patients	Single FQ prescriptions were not associated with FQ-resistant *M. tuberculosis*, whereas multiple FQ prescriptions imparted resistance
Chang *et al.*[196]	2010	Randomized open-label controlled trial, 427 patients	Newer FQs appeared to mask active pulmonary TB
Chen *et al.*[197]	2011	Meta-analysis of nine trials	Mean duration of delayed diagnosis and treatment of pulmonary TB in the FQ prescription group was 19.03 days; the odds ratio of developing fluoroquinolone-resistant *M. tuberculosis* strain was 2.7 (95% CI, 1.3–5.6)

Table 10: Doses of drugs used in CAP

Drug	Doses
Amoxicillin	0.5–1 g thrice daily (PO or IV)
Co-amoxiclav	625 mg thrice a day to 1 g twice daily (PO)/1.2 g thrice daily (IV)
Azithromycin	500 mg daily (PO or IV)
Ceftriaxone	1–2 g twice daily (IV)
Cefotaxime	1 g thrice daily (IV)
Cefepime	1–2 g two to three times a day (IV)
Ceftazidime	2 g thrice daily (IV)
Piperacillin–tazobactam	4.5 g four times a day (IV)
Imipenem	0.5–1 g three to four times a day (IV)
Meropenem	1 g thrice daily (IV)

outpatient without comorbidities (1A).

5. For outpatients with comorbidities [Table 8], oral combination therapy is recommended (β-lactams plus macrolides) (1A).
6. There is insufficient evidence to recommend tetracyclines (3B).
7. Fluoroquinolones should not be used for empiric treatment (1A).
8. Antibiotics should be given in appropriate doses to prevent emergence of resistance (1A).

Inpatient, non-ICU

9. The recommended regimen is combination of a β-lactam plus a macrolide (preferred β-lactams include cefotaxime, ceftriaxone, and amoxicillin–clavulanic acid) (1A).
10. In the uncommon scenario of hypersensitivity to β-lactams, respiratory fluoroquinolones (e.g. levofloxacin 750 mg daily) may be used if tuberculosis is not a diagnostic consideration at admission (1A). Patients should also undergo sputum testing for acid-fast bacilli simultaneously if fluoroquinolones are being used in place of β-lactams.
11. Route of administration (oral or parenteral) should be decided based upon the clinical condition of the patient and the treating physician's judgment regarding tolerance and efficacy of the chosen antibiotics (3A).

Inpatient, ICU

12. The recommended regimen is a β-lactam (cefotaxime, ceftriaxone, or amoxicillin–clavulanic acid) plus a macrolide for patients without risk factors for *P aeruginosa* (2A).
13. If *P. aeruginosa* is an etiological consideration, an antipneumococcal, antipseudomonal antibiotic (e.g. cefepime, ceftazidime, cefoperazone, piperacillin–tazobactam, cefoperazone–sulbactam, imipenem, or meropenem) should be used (2A). Combination therapy may be considered with addition of aminoglycosides/antipseudomonal fluoroquinolones (e.g. ciprofloxacin) (3A). Fluoroquinolones may be used if tuberculosis is not a diagnostic consideration at admission (1A). Patients should also undergo sputum testing for acid-fast bacilli simultaneously if fluoroquinolones are being used.
14. Antimicrobial therapy should be changed according to the specific pathogen(s) isolated (2A).
15. Diagnostic/therapeutic interventions should be done for complications, e.g. thoracentesis, chest tube drainage, etc. as required (1A).
16. If a patient does not respond to treatment within 48–72 h, he/she should be evaluated for the cause of non-response, including development of complications, presence of atypical pathogens, drug resistance, etc. (3A).

Treatment Protocol

What is the optimum duration of treatment?

Outpatients are effectively treated with oral antibiotics. Most non-severe infections would settle within 3–5 days. In ward patients, oral therapies may be given with a functional gastrointestinal tract, although initially the intravenous route is preferable. Patients may be switched to oral medications as soon as they improve clinically and are able to ingest orally. Early conversion to oral antibiotic is as effective as continuous intravenous treatment in moderate to severe CAP and results in substantial reduction in the duration of hospitalization.[103,206] Most patients respond within 3–7 days; longer durations are not required routinely. Also, short course treatment (≤7 days) has been found to be as effective as longer duration treatment, with no difference in short-term or long-term mortality, or risk of relapse or treatment failure.[207-209] Short-course treatment may, however, be suboptimal in certain situations such as meningitis or endocarditis complicating pneumonia, pneumococcal bacteremia, community-acquired methicillin-resistant *Sta. aureus* and atypical pathogens. Adequate studies on this issue

are lacking and decisions have to be individualized in the clinical context.[3,103,120]

When should patients be discharged?

Discharge may be contemplated when the patient starts taking oral medications, is hemodynamically stable, and there are no acute comorbid conditions requiring medical care. At least three recent meta-analyses have shown that short-term treatment (5–7 days) is as effective as conventional treatment (10–14 days), with decrease in the risk of adverse effects, duration of hospitalization, and no increase in mortality.[206,208,209]

Recommendations:

1. Switch to oral from intravenous therapy is safe after clinical improvement in moderate to severe CAP (2A).
2. Patients can be considered for discharge if they start accepting orally, are afebrile, and are hemodynamically stable for a period of at least 48 h (2A).
3. Outpatients should be treated for 5 days and inpatients for 7 days (1A).
4. Antibiotics may be continued beyond this period in patients with bacteremic pneumococcal pneumonia, *Sta. aureus* pneumonia, and CAP caused by *Legionella pneumoniae* and non–lactose-fermenting Gram-negative bacilli (2A). Antibiotics may also be continued beyond the specified period in those with meningitis or endocarditis complicating pneumonia, infections with enteric Gram-negative bacilli, lung abscess, empyema, and if the initial therapy was not active against the identified pathogen (3A).

Role of Biomarkers

The role of biomarkers as a means to guide the duration of antibiotic treatment has been in focus recently, with a slew of studies on this aspect. However, the methodology has hardly been consistent. Data for limiting the duration of treatment are insufficient. A single procalcitonin value at admission led to a reduction in the duration of antibiotics without a change in the mortality.[210] Same conclusions were arrived at in two meta-analyses.[211,212] Some biomarkers, especially procalcitonin, show promise, but data are still not available on the adequate use of these molecules.

Recommendation:

Biomarkers should not be routinely used to guide antibiotic treatment as this has not been shown to improve clinical outcomes (1A).

Adjunctive Therapies

What is the role of steroids?

Few studies advocate the use of steroids in severe CAP.[213-216] Other studies have argued against the use of steroids.[217-220] In a study of 213 patients, prednisolone 40 mg daily for 1 week did not improve outcome in hospitalized patients.[219] In a recent trial of dexamethasone in 304 patients, the use of dexamethasone reduced the length of hospital stay when added to antibiotic treatment in non-immunocompromised patients with mild to moderate CAP (6.5 vs. 7.5 days).[216] There is some benefit of steroids in CAP, but there is no significant reduction in mortality, and the increased risk of arrhythmias, upper gastrointestinal bleeding, and malignant hypertension may be possibly related to corticosteroids.[221] The use of glucocorticoids should be limited to patients with vasopressor-dependent septic shock and patients with early acute respiratory distress syndrome.[222-226]

What is the role of other adjunctive therapies?

There is no evidence to suggest the usefulness of treatments such as activated protein C, anticoagulants, immunoglobulin, granulocyte colony-stimulating factor, statins, probiotics, chest physiotherapy, antiplatelet drugs, cough medications, inhaled nitric oxide, angiotensin-converting enzyme inhibitors, and others in the routine management of CAP.[215,227-229] Noninvasive ventilation appears to be beneficial, and has the potential to reduce endotracheal intubation, shorten the ICU stay, and reduce the risk of death in the ICU if applied early in the course of CAP.[230]

Should ARDS/septic shock due to CAP be treated differently?

Patients with ARDS and septic shock secondary to CAP should be managed according to standard guidelines.[200,231] Noninvasive ventilation should be judiciously used in patients with ARDS.[232]

Recommendations:

1. Steroids are not recommended for use in non-severe CAP (2A).
2. Steroids should be used for septic shock or in ARDS secondary to CAP according to the prevalent management protocols for these conditions (1A).
3. There is no role of other adjunctive therapies (anticoagulants, immunoglobulin, granulocyte colony-stimulating factor, statins, probiotics, chest physiotherapy, antiplatelet drugs, over-the-counter cough medications, β_2 agonists, inhaled nitric oxide, and angiotensin-converting enzyme inhibitors) in the routine management of CAP (1A).
4. CAP-ARDS and CAP leading to sepsis and septic shock should be managed according to the standard management protocols for these conditions (1A).
5. Noninvasive ventilation may be used in patients with CAP and acute respiratory failure (2A).

Immunization

What is the role of immunization for prevention of CAP?

Most guidelines recommend immunization with pneumococcal and seasonal influenza vaccines for specific groups.[3,103,120] However, the adult immunization guidelines promulgated by the Association of Physicians in India do not recommend the use of these vaccines on a routine basis.[233] Pneumococcal vaccination (preferably at least 2 weeks prior to splenectomy) and one-time revaccination after 5 years was recommended in patients undergoing splenectomy. There was no evidence to support the efficacy of pneumococcal vaccine in preventing invasive pneumococcal disease in populations considered

at high risk, particularly healthy individuals aged ≥65 years living in institutions, patients suffering from chronic organ failure, patients with diabetes mellitus, nephrotic syndrome, or immunodeficiency. Pneumococcal vaccination has never been shown to consistently reduce the incidence of pneumococcal pneumonia; however, the incidence of invasive pneumococcal bacteremic disease is reduced.[234-245] Considering this, the use of pneumococcal vaccination is recommended in special high-risk groups [Table 11] but not as a routine in immunocompetent adults. Influenza vaccination is recommended routinely in all persons greater than 6 months of age. However, the success of vaccination depends on the presence of the prevalent strain in the vaccine. The use of influenza vaccination is based on the availability of regular data regarding the prevalent strains. There is insufficient data regarding the use of influenza vaccination in adults greater than 65 years of age.[246,247] The vaccine is especially recommended in high-risk groups.[236,242,246-250]

Recommendations:

1. Routine use of pneumococcal vaccine among healthy immunocompetent adults for prevention of CAP is not recommended (1A). Pneumococcal vaccine may be considered for prevention of CAP in special populations who are at high risk for invasive pneumococcal disease [Table 11] (2A).
2. Influenza vaccination should be considered in adults for prevention of CAP (3A).
3. Smoking cessation should be advised for all current smokers (1A).

HOSPITAL-ACQUIRED PNEUMONIA (HAP)/ VENTILATOR-ASSOCIATED PNEUMONIA (VAP)

Definitions

What is the definition of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)?

HAP is an inflammatory condition of the lung parenchyma, caused by infectious agents, neither present nor incubating at the time of hospital admission. It is defined as pneumonia developing 48 h after admission to the hospital.[251,252] HAP can further be classified as ICU HAP or non-ICU HAP depending upon whether this infection is acquired in the intensive care unit (ICU) or in other clinical areas (e.g. wards).[253] VAP is defined as pneumonia that develops in patients after 48 h of endotracheal intubation.[251,252] Patients who develop pneumonia while being assisted with non-invasive ventilation (NIV) are considered to have HAP rather than VAP as the upper airway defense mechanisms remain intact.

What is healthcare-associated pneumonia (HCAP)? Is it a distinct entity?

HCAP is a heterogeneous entity which includes pneumonia that occurs in the following patient populations: hospitalization in an acute care hospital for two or more days within 90 days of the infection, residence in a nursing home or long-term care facility, recent intravenous antibiotic therapy, chemotherapy, or wound care within 30 days of the current infection, and attendance at a hemodialysis clinic.[252] However, the definition of HCAP is not as well standardized or accepted as that of HAP or VAP. There is heterogeneity in defining HCAP amongst various studies and guidelines.[254]

Whether HCAP is a separate entity or a subgroup of CAP or HAP is currently unclear. This is further complicated by variability in defining HCAP in various studies. For example, the duration of preceding hospitalization has ranged from 30 to 360 days in various definitions.[254] Moreover, limited evidence exists on the relationship between prior antibiotic usage and prevalence of multidrug resistant (MDR) pathogens among individuals treated in primary care settings. Healthcare facilities and nursing homes cannot be considered a homogeneous environment with comparable prevalence of MDR pathogens. In the West, nursing homes generally provide long-term basic nursing and medical care with the option of further support if necessary. Similar healthcare establishments are rather uncommon in India. In the Indian setting, nursing homes generally represent private hospitals with smaller infrastructure. Nursing homes in India cannot be routinely considered as a risk factor for drug-resistant pathogens in all patients. Hence, the classification of HCAP is avoided in this document, and the selection of antimicrobial treatment should be judged on an individual basis.[255] The risk factors for acquiring infection with MDR pathogens are enumerated in Table 12.

Recommendation:

The risk stratification regarding acquisition of MDR pathogen should be individualized rather than using an umbrella definition of HCAP for this purpose (UPP).

Epidemiology

What is the burden and epidemiology of HAP/VAP?

HAP is the second most common nosocomial infection.[256] It is associated with a high morbidity and mortality.

Table 11: High-risk groups in whom vaccination is recommended

Pneumococcal disease
Chronic cardiovascular, pulmonary, renal, or liver disease
Diabetes mellitus
Cerebrospinal fluid leaks
Alcoholism
Asplenia
Immunocompromising conditions/medications
Influenza
Chronic cardiovascular or pulmonary disease (including asthma)
Chronic metabolic disease (including diabetes mellitus)
Renal dysfunction
Hemoglobinopathies
Immunocompromising conditions/medications
Compromised respiratory function or increased aspiration risk

Adapted from reference[103]

It prolongs the hospital stay and increases the cost of treatment. Overall burden is estimated at 5–10 cases per 1000 hospital admissions with a 6–20-fold increased risk of acquiring HAP/VAP in the mechanically ventilated patient.[257-259] HAP accounts for up to 25% of all ICU infections and more than 50% of the entire antibiotic prescriptions. The crude mortality rate for HAP may be as high as 30–70%, and attributable mortality has been estimated to vary between 33 and 50% in several studies.[252,260,261] The risk of HAP/VAP is the highest early in the course of hospital stay. The risk of developing VAP is estimated at around 3% per day during the first 5 days of ventilation, 2% per day during days 5–10 of ventilation, and 1% per day thereafter.[262,263] Approximately half of all episodes of VAP occur within the first 4 days of mechanical ventilation. The intubation process itself contributes to the risk of infection as evidenced by low occurrence of HAP in those noninvasively ventilated.[264]

The time of onset of pneumonia is an important epidemiologic consideration for acquisition of specific pathogens and outcomes in HAP. Early-onset HAP (and VAP) is defined as pneumonia occurring within the first 4 days of hospitalization (or endotracheal intubation).[265] It usually carries a better prognosis and is more likely to be caused by antibiotic-sensitive bacteria. Late-onset HAP and VAP (day 5 or thereafter) are more likely to be caused by MDR pathogens, and are associated with higher morbidity and mortality. However, patients with early-onset HAP who have received prior antibiotics or who have been recently hospitalized may be at a greater risk for colonization and infection with MDR pathogens.[252,266]

The incidence of VAP as reported in various Indian studies ranges from 16 to 53.9% [Table 13].[267-271,272,273,274] Although these data are limited and heterogeneous, the general incidence appears fairly high. Most Indian data on HAP/VAP originates from tertiary hospitals and medical ICUs and may not be truly representative of other settings. For instance, HAP may be more common than presumed in wards or other ICU areas.

Table 12: Risk factors for infection with MDR bacteria

Antimicrobial therapy in the preceding 3 months
Present hospitalization of ≥5 days
High frequency of antibiotic resistance in the community or in the specific hospital unit
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
Immunosuppressive drug and/or therapy

*Adapted from reference[252]

How is the organism profile in Indian settings different from the Western data?

HAP and VAP are caused by a wide spectrum of bacterial pathogens and may be polymicrobial. Common pathogens include aerobic Gram-negative bacilli such as *P. aeruginosa, E. coli, K. pneumoniae,* and *Acinetobacter* species. Infections due to Gram-positive cocci, such as *Sta. aureus,* particularly methicillin-resistant *Sta. aureus* (MRSA), are rapidly emerging in the West. Pneumonia due to *Sta. aureus* is reportedly more common in patients with diabetes mellitus, head trauma, and those hospitalized in ICUs.[252,261,266] On the other hand, Gram-negative pathogens still remain the most common organisms responsible for causing HAP/VAP in most Indian reports.[270,272-274] Most studies report *Acinetobacter* species followed by *P. aeruginosa* as the most common organisms isolated from patients having HAP/VAP.

Does the microorganism profile vary amongst different centers and within the same hospital setting?

The rates of acquiring infection with MDR pathogens have drastically increased over the past few years.[252] The type of MDR pathogens causing HAP may vary by hospital, patient population, exposure to antibiotics, type of ICU, and changes over time, emphasizing the need for constant local microbiological data. The microbial etiology of VAP appears to differ even between different hospitals within the same city and between ICUs within a single hospital. The empiric antibiotic treatment decisions for patients with VAP must take into account local microbiology and antimicrobial susceptibility profile.[252,257,261,275]

Recommendation:

Gram-negative bacteria are the most common pathogens causing HAP/VAP in the Indian setting (UPP) and should be routinely considered as the most common etiological agents of HAP/VAP.

Table 13: Studies reporting the incidence of HAP/VAP from the Indian subcontinent

Study	Year	Type of study	Duration	Diagnostic criteria	Type of patient	CFU/ml	No. of patients	Incidence of VAP (%)	Mortality (%)
Mukhopadhyay *et al.*[267]	2003	Prospective	1 year	Clinical, PSB, BAL	Surgical ICU	$\geq 10^5$	241	53.9	47.3
Rakshit *et al.*[268]	2004	Prospective	1 year	Clinical	Cardiac ICU	-	51	47	37
Singhal *et al.*[269]	2005	Retrospective	1 year	Non-bronchoscopic BAL	ICU	$\geq 10^4$	478	35.77	-
Agarwal *et al.*[270]	2006	Prospective	1.5 years	Clinical, ETA	ICU	$\geq 10^5$	201	23	-
Prakash *et al.*[271]	2008	Prospective	1 year	Clinical, BAL	ICU	Semi-quantitative	50	50	-
Joseph *et al.*[272]	2009	Prospective	15 months	Clinical, ETA	Medical ICU	$\geq 10^5$	1248	16	-
Bajpai *et al.*[273]	2010	Prospective	3 years	Clinical, mini-BAL	Medical ICU	Quantitative and semi-quantitative	248	19	-

Diagnosis

When should HAP/VAP be suspected?

HAP/VAP should be suspected in any hospitalized/ventilated patient with symptoms and signs of pneumonia. Sensitive criteria based on clinical and radiologic parameters should be used to enable early diagnosis.[276] The following findings suggest the presence of HAP/VAP in any patient who has been hospitalized or is being mechanically ventilated and include new or progressive radiologic deterioration along with two of the following: new onset fever, purulent secretions, leukocytosis, and decline in oxygenation.[252,277] Patients with ARDS may be suspected as harboring VAP if there significant decline in oxygen status as indicated by: (a) sustained increase in positive end-expiratory pressure (PEEP) requirement by ≥2.5 cm H_2O after being stable or decreasing or (b) FiO_2 requirements rise by ≥0.15 after being stable or decreasing.[277] The Centers for Disease Control (CDC) criteria are widely used in the diagnosis of HAP [Table 14].[278]

What is the approach to diagnose HAP/VAP?

The purpose of diagnostic techniques is: (a) to determine whether a patient has pneumonia and (b) to identify the etiological pathogen. An appropriate diagnostic algorithm involves collection of pertinent clinical samples for bacterial cultures, early institution of effective antibiotic therapy, and provision for de-escalation whenever possible. Most of the available literature and guidelines focus on VAP, and very little data are available for HAP. The diagnostic approach revolves around two strategies: the clinical strategy and the bacteriological strategy.[252,253]

Clinical strategy

The clinical strategy combines clinical suspicion with semi-quantitative cultures of sputum and/or tracheal aspirates. Clinical parameters include fever, pulmonary manifestations (e.g. purulent sputum or endotracheal secretions, abnormal respiratory system examination, worsening gas exchange), and basic investigations (e.g. leukocytosis, abnormal chest radiograph). Advanced radiologic investigations such as CT scanning are neither feasible in most patients nor recommended. Clinical data are supplemented by microbiological workup.

Table 14: Modified CDC criteria for diagnosis of HAP/VAP

Chest radiographic opacities (new, progressive, or persistent infiltrate or cavitation) and at least two of the following:
Fever >38°C or >100.4°F
Leukopenia (<4000 WBC/μL) or leukocytosis (≥12,000 WBC/μL)
Altered mental status with no other recognized cause in the elderly
New onset of purulent sputum, or change in character of sputum, or increased respiratory secretions, or increased suctioning requirements
Worsening gas exchange (e.g. desaturations, increased oxygen requirements, or increased ventilator demand)
New onset or worsening cough, or dyspnea, or tachypnea
Rales or bronchial breath sounds

Adapted from reference[278]

Sputum or endotracheal aspirates (ETAs) are easily obtained in most patients and should be sent for culture before initiation of antibiotics. It is important to ensure that a representative sample of the lower respiratory tract is collected. Despite its numerous limitations, sputum appears to be the only representative lower respiratory tract sample in non-intubated patients. Routine culture reporting as either positive or negative is not useful since it cannot discriminate at all between the wide spectrum of light contamination and heavy infection. Semi-quantitative cultures overcome this problem to some extent, and are still technically simple enough to be feasible in most standard microbiology laboratories. Culture growths are reported semi-quantitatively as light, moderate, or heavy. Semi-quantitative tracheal aspirate cultures are highly sensitive, but have low specificity and cannot differentiate colonization from infection. However, their specificity increases when combined with clinical criteria.[252,277] The semi-quantitative cultures, however, have a high negative predictive value. In fact, a sterile ETA culture is strong evidence against pneumonia in the absence of a recent change in antibiotic therapy.[279] In addition, blood cultures, as well as cultures of other clinical specimens (such as pleural fluid) should also be submitted. These additional investigations help in identifying possible extrapulmonary sites of infection, and a concordant isolate from both respiratory and other samples virtually clinches the microbial etiology.

It must be emphasized that a combination of clinical and radiologic features alone has low specificity for diagnosing HAP/VAP due to substantial overlap with non-infectious conditions like congestive heart failure, pulmonary edema, pulmonary hemorrhage, atelectasis, and others.[280] Therefore, supplementary microbiological data are extremely important. No single constellation of clinicoradiological findings is a perfect diagnostic marker of HAP/VAP. There have been several efforts to formulate objective bedside criteria to assist the clinician in diagnosing HAP/VAP. One widely used clinical approach is the CDC algorithm for "clinically defined pneumonia," which attempts diagnosis based on the presence of two of three radiologic criteria, plus at least one systemic and two pulmonary signs clinically suggestive of pneumonia [Table 14].[278]

Table 15: Modified Clinical Pulmonary Infection Score[281]

CPIS points	0	1	2
Tracheal secretions	Rare	Abundant	Abundant and purulent
Chest X-ray infiltrates	No infiltrates	Diffuse	Localized
Temperature (°C)	≥36.5 and ≤38.4	≥38.5 and ≤38.9	≥39 or ≤36
Leukocytes (per mm^3)	≥4000 and ≤11,000	<4000 or >11,000	<4000 or >11,000 plus band forms ≥500
PaO_2/FiO_2 ratio	>240 or ARDS		≤240 and no evidence of ARDS
Microbiology	Negative		Positive

A score of more than 6 at baseline or after incorporating the Gram stains (CPIS gram) or culture (CPIS culture) results is suggestive of pneumonia

In order to increase the specificity of clinical diagnosis, the clinical pulmonary infection score (CPIS) is utilized, which combines clinical, radiographic, physiological (PaO2/FiO2), and microbiological data into a single numerical result [Table 15].[281-284] When the CPIS exceeded 6, good correlation was found with pneumonia diagnosed by quantitative cultures of bronchoscopic and non-bronchoscopic bronchoalveolar lavage (BAL) specimens.[282] Singh and colleagues also proposed a modified CPIS that does not rely on culture data to guide clinical management.[284] Not all recent studies have corroborated the high accuracy initially reported for the CPIS.[285] The accuracy of the CPIS is not high without microbiological data, but can be improved if a reliable lower respiratory tract sample is obtained and studied carefully using Gram staining.[286,287] Although CPIS may not be a good tool for diagnosis of HAP/VAP, it may still help the clinician to evaluate the clinical response to therapy and determine its appropriate duration. The duration of therapy was directly correlated with the CPIS at the time of pneumonia diagnosis. In one study, the CPIS when calculated prospectively and used serially throughout the course of VAP management, decreased in patients who survived, but not in those who did not, thus reflecting the clinical evolution of pneumonia.[288] It is therefore also important that if clinical/microbiological features do not objectively support infection but the clinical suspicion of HAP/VAP is high, patient may be reevaluated after 48–72 h.

Recommendations:

1. HAP/VAP can be clinically defined [Figure 2] using modified CDC criteria (2A).
2. In patients with a strong suspicion of VAP/HAP but insufficient evidence for the presence of infection, periodic reevaluation should be done (2A).
3. In patients with suspected VAP/HAP, one or more lower respiratory tract samples and blood should be sent for cultures prior to institution of antibiotics (1A).
4. All patients suspected of having HAP should be further evaluated with good-quality sputum microbiology (3A).
5. CT scan should not be routinely obtained for diagnosing HAP/VAP (3A).
6. Semi-quantitative cultures can performed in lieu of qualitative cultures (1A).
7. Appropriate management should not be delayed in clinically unstable patients for the purpose of performing diagnostic sampling (UPP).

Bacteriological strategy

The bacteriological strategy depends upon "quantitative" cultures of lower respiratory secretions {ETA [10^5 or 10^6 colony forming units (CFU)/mL], bronchoalveolar lavage [BAL, 10^4 CFU/mL] or protected-specimen brush [PSB, 10^3 CFU/mL] specimens, collected with or without a bronchoscope} to establish both the presence of pneumonia and the etiological pathogen. Growth above a threshold concentration is necessary to determine the causative microorganism. The threshold is obtained through cultures of serial dilutions of the clinical material, and is described in terms of CFU per unit volume of the undiluted sample. Bacteriological approach gives importance to separating colonizers from infecting pathogens.[289-291] However, such an approach is technically demanding, both in terms of equipment/accessories needed for sample collection and the infrastructure required for microbiological standardization. There is hardly any microbiology laboratory in India that routinely performs quantitative cultures, and quantitative cultures are considered more of a research tool.[292] The bacteriological strategy is considerably more expensive in terms of sampling and diagnostics, but may reduce the overall cost of treatment as fewer patients (only microbiologically confirmed pneumonia) are treated with targeted antibiotic therapy.

In several studies, the sensitivity of quantitative tracheal aspirate samples has been >80% for identifying an etiological pathogen, results that were often comparable to bronchoscopic findings in the same patients.[252,293-296] The quality of the PSB sample is difficult to measure and the reproducibility is not exact, with as many as 25% of results on different sides of the diagnostic threshold when comparing two samples collected from the same site in the same patient.[296,297]

Are quantitative methods of culture better than semi-quantitative methods?

The value of quantitative cultures in clinical settings would be negated if there were a high rate of false-positive or false-negative findings. False-positive results would mean that patients without VAP are erroneously diagnosed. This could prove harmful because of resulting overtreatment and can hamper evaluation of the true efficacy of antibiotics. False-positive results have been reported for patients receiving prolonged mechanical ventilation, who are often colonized at high bacterial concentrations.[298] Similarly, a false-negative quantitative culture result means that some patients with VAP are missed. This is possible as many patients with suspected VAP are on antibiotic therapy. Although this is a common concern, it may be less of a consideration if the patient had been receiving the same therapy for at least 72 h before diagnostic samples are obtained.[299] There is no difference in terms of mortality, ICU stay, duration of mechanical ventilation, or rates of antibiotic change when either technique was used for diagnosing HAP/VAP. Quantitative and semi-quantitative cultures, of blind or targeted lower respiratory secretions, have equivalent yield and clinical utility.[300-302]

Recommendation:

Semi-quantitative cultures of lower respiratory tract secretions are easier and equally discriminatory for the presence of pneumonia, as compared to quantitative cultures (UPP).

Are invasive techniques to collect lower respiratory tract secretions better than blind endotracheal aspirates?

The lack of a well-established gold standard remains a challenge in the diagnosis of HAP/VAP. To counter

contamination of respiratory secretions, it has been suggested that invasive methods, including bronchoscopy-directed BAL or PSB, or protected BAL or PSB can improve the diagnostic yield over blind ETA, and guide appropriate antibiotic selection. However, results of various comparative studies are inconclusive.[252] Although an initial study suggested lower mortality with the invasive strategy,[280] subsequent studies have failed to demonstrate these results.[300,303] The use of bronchoscopy to collect lower respiratory tract secretions requires additional expertise, which may not be available at all hospitals, and also considerably increases the cost due to expensive accessories required for this purpose. To limit contamination and aspirate secretions from more distal portions, simple telescoping catheter systems can be easily devised using indigenous components, and used to collect more representative and higher-quality specimens in a blind fashion.[297] Quantitative or semi-quantitative cultures can be performed on ETA or samples collected either bronchoscopically or non-bronchoscopically. Each technique has its own diagnostic threshold and methodological limitations. The choice depends on local expertise, availability, and cost.

Recommendations:

1. Quantitative and or semi-quantitative cultures using various sampling techniques like ETA, bronchoscopic or non-bronchoscopic BAL and PSB are equally useful for establishing the diagnosis of HAP/VAP (2A).
2. Semi-quantitative culture on blind (non-bronchoscopic) ETA sample (preferably obtained through a sterile telescoping catheter system) is a reasonable choice (2A).
3. In a patient suspected of having VAP, the preferred method for lower respiratory tract sample collection (blind or targeted, bronchoscopic or non-bronchoscopic) depends upon individual preferences, local expertise, and cost; however, blind ETA sampling is the easiest and equally useful (UPP).

What is the role of biomarkers in diagnosis of HAP/VAP?

An ideal biomarker for VAP should not be detectable when infection is not present, and should be elevated in the presence of infection. Three biomarkers have been studied extensively for predicting VAP: soluble triggering receptor expressed on myeloid cells type 1 (sTREM-1), PCT, and CRP.[304-314] None of the currently available biomarkers has good utility for diagnosis of HAP/VAP. However, PCT can be utilized to differentiate bacterial VAP from non-infective causes of pulmonary infiltrates and to take decisions about stopping antibiotics in the ICU.

Recommendations:

1. Currently available biomarkers should not be used to diagnose HAP/VAP (1A).
2. Where available, serum procalcitonin levels <0.5 ng/mL may help in differentiating bacterial HAP/VAP form other non-infective etiologies, and may help in decisions for antibiotic cessation (2B).

Is combined clinicobacteriological strategy better than either strategy used alone?

Beyond issues with the sensitivity and specificity of the CPIS, inter-observer variability in noting clinical parameters remains a major concern, as different clinicians may not absolutely concur with the clinical features in a given patient.[285] Adding microbiological results improves this situation by providing objective evidence of infection. A predominantly clinical approach involves empiric antibiotic therapy in those clinically diagnosed as having pneumonia and can thus result in overtreatment. A bacteriological approach, on the other hand, recommends antibiotics only to those in whom pneumonia is microbiologically confirmed. However, quantitative cultures are not routinely available, and the strategy can result in denying treatment to those with false-negative cultures. A combined approach is logically attractive, with a primary goal of using appropriate therapy in a timely manner, without overusing antibiotics [Figure 2].

In a combined approach, patients strongly suspected to have HAP/VAP undergo lower respiratory tract sampling. Empiric antibiotics may be started after specimens have been submitted for culture. For patients highly suspected to have pneumonia but not fulfilling the essential clinical criteria for the same, regular monitoring is advocated. Some of these patients may actually have ventilator-associated tracheobronchitis (VAT), which is defined by the presence of fever, increased volume and purulence of respiratory secretions, a positive culture of a respiratory sample, and the absence of a new or an evolving pulmonary infiltrate in the chest X-ray in a patient on mechanical ventilation for >48 h.[315,316] VAT is distinct from VAP, and not all experts advocate antibiotic usage in this situation. If patients deteriorate subsequently and fulfill the diagnostic criteria for pneumonia, they can be managed as above. In either situation, the decision to continue/modify/stop antibiotics can be taken once culture results are available, taking into account the overall clinical features and response to treatment. Several guidelines advocate the use of a combined clinical and bacteriological strategy for better outcomes in diagnosing and treating HAP/VAP.[252,253]

Recommendation:

Both clinical and bacteriological strategies can be combined to better diagnose and manage HAP and VAP (UPP).

Treatment

What are the general principles of managing HAP/VAP?

Once HAP/VAP is suspected, antibiotics should be initiated as soon as possible after taking adequate specimens for microbiological culture. The empiric antibiotic choice is based on the timing of development of HAP and assessment of the patient's risk for MDR pathogens [Figure 3]. Early-onset HAP is arbitrarily classified as pneumonia developing within the first 4 days of hospitalization and late-onset HAP as pneumonia 5 or more days after hospitalization. However, many patients are admitted in other hospitals before being transferred, hence this duration should be

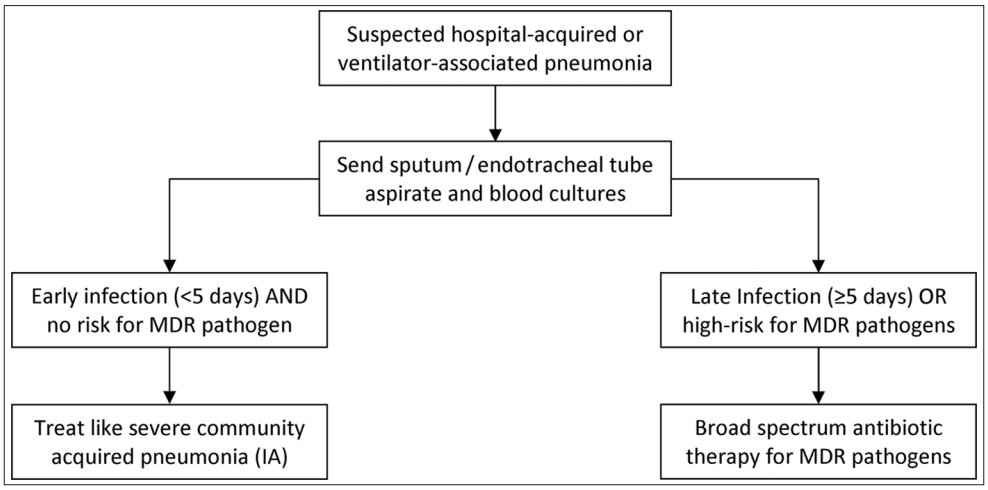

Figure 3: Assessment of the risk of MDR pathogens in HAP/VAP

kept in mind while deciding the empiric antibiotic therapy. As the treatment is started empirically, the initial cover is generally broad spectrum, and hence all efforts should be made to de-escalate antibiotics once culture reports are available.

What are the characteristics of empiric combination therapy for the treatment of VAP/HAP?

The empiric combination therapy should be appropriate, adequate, and optimal. The term "appropriate" means the chosen empiric antibiotic therapy should cover the organism which would eventually be isolated. The odds of mortality are higher in patients receiving initial inappropriate antibiotic therapy.[317-321] An "adequate" antibiotic therapy ensures proper route of administration and proper penetration of the drug, and an "optimal" antibiotic regimen means that the antibiotic dosage should be according to the pharmacokinetics and pharmacodynamics of the chosen drug.

How do we decide on the empiric antibiotic regimen to be started in a case of suspected HAP/VAP?

Every hospital/ICU should have its own written antibiotic policy to initiate empiric antibiotic therapy in suspected nosocomial pneumonia. Any deviation from the policy should be based on strong evidence. Formulation of antibiotic policy should be based on the antibiogram, which is updated as often as possible, and at least once over the previous 6 months. The antibiogram can be periodically changed according to the reports obtained. In the absence of a hospital or ICU antibiotic policy, these guidelines should be employed for the initial empiric therapy.

Recommendations:

1. Every ICU/hospital should have its own antibiotic policy for initiating empiric antibiotic therapy in HAP based on their local microbiological flora and resistance profiles (1A). This policy should be reviewed periodically.
2. In hospitals that do not have their own antibiotic policy, the policy given in these guidelines is recommended (3A). However, they should strive toward formulating their own antibiotic policy.

What is the role of routine endotracheal aspirate culture surveillance?

Routine endotracheal aspirate culture surveillance (REAS) is performed by obtaining serial endotracheal aspirate cultures at fixed intervals even in the absence of infection. The results of the cultures obtained are then employed in guiding the antibiotic regimen if the patient develops evidence of HAP. Although some studies suggest the usefulness of this strategy with high concordance between the surveillance culture and the organism subsequently identified during VAP,[322,323] others indicate a limited role.[324] As this strategy is more expensive than the antibiogram strategy, it is not feasible in developing countries.

Recommendation:

Routine endotracheal aspirate culture is not recommended. An antibiogram approach should be followed wherever feasible (2A).

Is there a benefit of combination therapy over monotherapy for the treatment of HAP/VAP and HCAP?

Various societies have given recommendations for deciding on the empiric regimen.[253,325-331] Most guidelines recommend monotherapy if there are no risk factors for MDR pathogens and combination therapy if there are risk factors for MDR pathogens, except for the British Thoracic Society guidelines which recommend monotherapy for MDR pathogens as well.[326] There is evidence both for and against combination therapy. The combination therapy carries a higher chance of the empiric regimen being appropriate and of antibacterial synergy between compounds. However, combination therapy also entails the risks of adverse effects related to therapy, increased emergence of drug-resistant organisms, and increased cost of therapy. There is no conclusive evidence in favor of either combination or monotherapy in several trials and meta-analyses.[332-337]

Recommendation:

Although there is no evidence to suggest that combination therapy is superior to monotherapy, the expert group recommended initial empiric therapy as a combination due to the high prevalence rates of MDR pathogens in late-onset HAP/VAP [Table 16] and with an aim to ensure the chances of appropriateness of the initial regimen (UPP). However, once the culture reports are available, the regimen should be de-escalated to the appropriate monotherapy (1A).

What is the recommended strategy for initiating antibiotics in suspected HAP/VAP?

Antibiotics should be initiated as soon as possible after sending the appropriate microbiological samples as delay in initiation of appropriate antibiotic therapy has also been associated with increased mortality.[338-347] The initial empiric antibiotic therapy should generally cover the MDR pathogen, and should be initiated with an antipseudomonal penicillin, cephalosporin, or carbapenem, along with an aminoglycoside [Table 16]. The exact choice of antibiotic depends on local availability, antibiotic resistance patterns, preferred routes of delivery, other complicating factors, and costs. Fluoroquinolones should be used only in those with contraindications to aminoglycosides so as to reserve the use of fluoroquinolones for the treatment of TB and decrease the probability of emergence of fluoroquinolone-resistant *M. tuberculosis*. The initial combination therapy should be converted to appropriate monotherapy once culture reports become available. Empiric therapy for MRSA initially is not recommended due to the low prevalence of MRSA in the Indian ICUs; if there is a documented high prevalence of MRSA, the initial empiric therapy should also cover MRSA. Polymyxins are not recommended as empiric therapy in the treatment of HAP/VAP. A combination of meropenem and colistin is being increasingly used in the community despite a study documenting increased mortality with this combination.[348]

Recommendations:

1. In patients with suspected HAP, antibiotics should be initiated as early as possible after sending the relevant samples for culture (1A).
2. The exact choice of antibiotic to be started is based on local availability, antibiotic resistance patterns, preferred routes of delivery, other complicating factors, and cost.
3. The initial combination therapy should be converted to appropriate monotherapy once culture reports are available (1A).
4. Colistin is not recommended as an initial empiric therapy for HAP/VAP (3A).
5. Combination therapy with colistin and meropenem is not recommended (2A).

Table 16: Initial empiric therapy in patients with late-onset HAP/VAP

Organisms to cover: *Acinetobacter* spp., *P. aeruginosa*, ESBL producing *E. coli*, and *K. pneumoniae*
Initiate therapy with any one of the following (1A):
• Antipseudomonal penicillins or third- or fourth-generation cephalosporins (cefoperazone–sulbactam/cefepime/cefpirome/piperacillin–tazobactam/ticarcillin–clavulanate
• Antipseudomonal carbapenems (meropenem/imipenem)
• Monobactam (aztreonam)
Plus
• Aminoglycoside (amikacin/gentamicin/tobramycin) or
• Fluoroquinolone (ciprofloxacin/levofloxacin)
Add MRSA cover only if ICU flora shows high prevalence of MRSA (1A):
• Vancomycin or Teicoplanin
General principles
• Switch to monotherapy as soon as the culture reports are available
• If the culture is negative, continue aminoglycoside or fluoroquinolone for 5 days

Is antibiotic de-escalation useful? What is the strategy for antibiotic de-escalation?

Antibiotic de-escalation is defined as the shift from broad-spectrum to narrow-spectrum antibiotic once the culture reports become available, to stop antibiotics if no infection is established or to shift from combination to monotherapy, whenever possible.[349] The benefits include: (a) improved or unaltered treatment outcomes; (b) decrease in antimicrobial resistance; (c) decrease in antibiotic-related side effects; (d) decrease in superinfections; and (e) reduction in overall antibiotic costs.[350] Cessation of antibiotics after 3 days when the CPIS was <6 did not alter the mortality and length of ICU stay.[284] Numerous studies have shown improved or unchanged outcome with the de-escalation strategy.[351-358]

Recommendations:

1. The strategy for de-escalation of antibiotics is strongly recommended (1A). However, as the de-escalation strategy entirely rests on microbiology, appropriate microbiological samples should be sent before initiation of antibiotics [Figure 2].
2. Among patients with suspected VAP in whom an alternate cause for pulmonary infiltrates is identified, it is recommended that antibiotics should be stopped (1A).
3. If cultures are sent after initiation of antibiotics and there is clinical improvement with subsequent cultures being sterile, antibiotics should be continued for 7 days followed by assessment of CPIS on the 7th day. If CPIS is <6, antibiotics can be stopped, while if it is ≥6, treatment should be continued for 10–14 days.
4. If cultures sent before starting antibiotics are negative and there is clinical worsening, it is recommended that a review of the current management plan including the choice of antibiotics be performed. Microbiological workup should be repeated including performance of fungal cultures. One also needs to look for alternate sources of sepsis (especially one or more foci of undrained infection) and consider non-infective causes.
5. Empiric antifungal therapy (on day 3) should not be used as a routine in all patients if cultures are sterile and there is clinical worsening (3A).

What is the optimal duration of antibiotic therapy?

In a study comparing 8 versus 15 days of antibiotic therapy in VAP, there were more antibiotic-free days, decreased

risk of super infections with MDR pathogens, no increased mortality, no recurrent infections, and no change in duration of mechanical ventilation or ICU stay in the 8-day treatment group.[290] Only patients with *Pseudomonas* infection had increased recurrence of pneumonia. Another study has shown that the fall in CPIS on 3rd and 5th day was significant in survivors compared to non-survivors.[288] This study also suggests that serial monitoring of CPIS could identify those patients with good outcomes and help in shortening the duration of treatment. Various societies have recommended short-course treatment (7–8 days) for the management of VAP if the organism is not non–lactose-fermenting Gram-negative bacteria or *P. aeruginosa*.[253,325-328]

Recommendations:

1. In patients with VAP due to *Pseudomonas*, *Acinetobacter*, and MRSA, a longer duration (14 days) of antibiotic course is recommended (1A). Assessment of CPIS on day 7 may identify the patients in whom therapy could be stopped early (2A).
2. In other patients with VAP who are clinically improving, a 7-day course of antibiotics is recommended (1A).

Is continuous infusion of antibiotics better than intermittent doses?

The decision to give continuous infusions or intermittent doses depends on whether the antibiotics being administered follow time-dependent or concentration-dependent kinetics or both.[359,360] Time-dependent antibiotics require drug concentrations greater than the minimum inhibitory concentration or MIC (T > MIC) for a certain period of time between doses, which usually ranges from 40 to 50% of inter-dose interval for their best action. The examples include β-lactams, carbapenems, and lincosamides. These drugs are best given as continuous infusions over a particular duration depending on the stability of the prepared drug at room temperature. On the other hand, concentration-dependent antibiotics like aminoglycosides are best administered as a single daily dose or as intermittent doses. These antibiotics require attainment of peak concentration many times higher than the MIC for their best action and have prolonged post-antibiotic effect (PAE) which makes them effective even after their drug concentration falls below the MIC. Concentration- and time-dependent antibiotics (fluoroquinolones and glycopeptide antibiotics) require both time as well as concentration for their optimal action. The area under the concentration time curve (AUC)/MIC determines the clinical efficacy of these antibiotics. A lower 14-day mortality (12.2 vs. 31.6%) and lower mean duration of hospital stay (21 vs. 38 days) was seen among patients with APACHE II scores ≥17 receiving extended infusions.[361] Several other studies have demonstrated that continuous infusions are associated with numerous clinical benefits including decrease in hospital stay and mortality.[362-366]

Recommendation:

Antibiotic administration in critically ill patients is recommended according to their pharmacokinetic/pharmacodynamic profile [Table 17] as it is associated with superior clinical outcomes (2A).

Table 17: Doses of intravenous antibiotics used in the treatment of HAP/VAP

β-lactam/β-lactamase inhibitors	
Piperacillin–tazobactam	4.5 g IV four to six times a day (4-h infusion)
Cefoperazone–sulbactam	2–3 g IV two to three times a day (3-h infusion)
Ticarcillin–clavulanate	3.1 g IV three to four times a day (3-h infusion)
Carbapenems	
Meropenem	1 g IV thrice daily (3-h infusion)
Imipenem	0.5–1 g IV four times a day (2-h infusion)
Antipseudomonal cephalosporins	
Cefepime	2 g IV two to three times a day (3-h infusion)
Cefpirome	2 g IV two to three times a day (3-h infusion)
Antipseudomonal quinolones	
Ciprofloxacin	400 mg IV thrice daily over 30 min
Levofloxacin	750 mg IV daily over 30 min
Antipseudomonal aminoglycosides	
Amikacin	20 mg/kg IV daily over 30 min
Netilmicin	7 mg/kg IV daily over 30 min
Tobramycin	7 mg/kg IV daily over 30 min
Anti-MRSA drugs	
Vancomycin	500 mg IV four times a day (4-h infusion)
Teicoplanin	12 mg/kg loading dose followed by 6–12 mg/kg daily (4-h infusion)
Linezolid	600 mg twice daily over 30 min
Polymyxins	
Colistin	6–9 MU/day in divided doses
Polymyxin B	15,000–25,000 U/kg/day IV twice daily

Antibiotic doses should be adjusted according to GFR and ideal body weight except in those with morbid obesity where the dose is calculated as follows: (actual body weight + ideal body weight)/2

What is the role of inhaled antibiotics in the treatment of VAP?

Inhaled antimicrobials may be as safe and as efficacious as standard antibiotics for the treatment of VAP.[367] In fact, aerosolized vancomycin and gentamicin have been shown to decrease VAP, facilitate weaning, reduce bacterial resistance, and the use of systemic antibiotics when used in those with ventilator-associated tracheobronchitis.[368] Patients receiving adjunctive aerosolized antibiotics had higher 30-day survival.[369] Recently, nebulized colistin when added to intravenous colistin has been associated with better microbiological outcome (60.9 vs. 38.2%) although the clinical outcomes were similar.[370] Another retrospective cohort study suggested that the clinical cure rates are better when colistin is given simultaneously in both intravenous and inhaled forms.[371] Several smaller retrospective observational studies have shown better clinical response with the combination of intravenous and inhaled antibiotics,[372-374] while some others have used aerosolized colistin monotherapy for treatment of MDR pathogens with good clinical outcomes.[375-377] However, all the aforementioned reports are anecdotal with small sample size; hence, more data are required before the routine use of inhaled antibiotics can be recommended.

Recommendations:

1. Aerosolized antibiotics (colistin and tobramycin) may be a useful adjunct to intravenous antibiotics in the

treatment of MDR pathogens where toxicity is a concern (2A).
2. Aerosolized antibiotics should not be used as monotherapy and should be used concomitantly with intravenous antibiotics (2A).

Should one treat ventilator-associated tracheobronchitis?

Ventilator-associated tracheobronchitis (VAT) is defined as the presence of elevated temperature (>38°C), leukocytosis (>12,000/μL)/leukopenia (<4000/μL) plus a change in quantity or quality (purulent) of endotracheal secretions without new radiologic infiltrates.[378] This usually, but not necessarily, is accompanied by demonstration of bacteria on Gram stain or semi-quantitative cultures of endotracheal aspirate. VAT has been associated with longer duration of mechanical ventilation and ICU stay among patients without chronic respiratory failure.[379] Administration of systemic antimicrobials with or without concurrent inhaled drug decreases neither the mortality nor the ICU stay or the duration of mechanical ventilation.[380] There is no clear-cut evidence of benefit with treatment of VAT, and treatment of VAT is usually not recommended. However, these patients should be re-evaluated as required for the development of VAP.

Recommendation:

Patients with proven VAT should not be treated with antibiotics (2A).

What are the drugs of choice for treatment of methicillin-resistant Staphylococcus aureus?

Drugs approved for the treatment of MRSA pneumonia include vancomycin, teicoplanin, and linezolid. Newer investigational drugs include lipoglycopeptides (telavancin, dalbavancin, and oritavancin), cephalosporins (ceftobiprole and ceftaroline), and dihydrofolate reductase inhibitors (iclaprim).[381] Vancomycin has certain drawbacks such as poor lung tissue penetration, potential nephrotoxicity, and inferior clinical outcomes.[382] Linezolid has been suggested as a better choice in the management of MRSA pneumonia. Two meta-analyses found no difference in clinical cure rates and microbial eradication rates between vancomycin and linezolid,[383,384] although a recent randomized clinical trial (RCT) showed that clinical response was significantly higher with linezolid compared to vancomycin, but with no difference in mortality.[385]

Recommendations:

1. In patients with suspected MRSA infection, we recommend the use of empiric vancomycin (1A) or teicoplanin (2A). The use of linezolid in India should be reserved because of its potential use in extensively drug-resistant tuberculosis.
2. Linezolid is an effective alternative to vancomycin (1A) if the patient (a) is vancomycin intolerant, (b) has renal failure, and (c) is harboring vancomycin-resistant organism.

How to treat MDR Acinetobacter infections?

The treatment options for MDR *Acinetobacter* include carbapenems, polymyxins [polymyxin B and polymyxin E (colistin)], tigecycline, and combination therapy with sulbactam or rifampicin, or combination of carbapenem with colistin.[386] Colistin is as safe and as efficacious as the standard antibiotics for the treatment of VAP.[387] Although the recommended dose of colistin is 2 MU intravenously thrice a day, some studies suggest using higher doses of colistin (9 MU/day) as the concentration is higher than the MIC breakpoint (2 mg/mL) at this dose.[388-390] Good outcomes have been noted in majority of the patients treated with polymyxin B.[391]

Combination of colistin and imipenem was synergistic in 50% of colistin-susceptible imipenem-resistant *K. pneumoniae* strains.[392] No difference in clinical response and nephrotoxicity was observed in one retrospective study.[348] In fact, the survival was lower in patients with combination therapy.

Sulbactam is a relatively new agent for the treatment of MDR *Acinetobacter*. Several *in vitro* and *in vivo* animal studies reported intrinsic activity of sulbactam against *Acinetobacter*.[393,394] The recommended dose for sulbactam is 40–80 mg/kg (at least 6 g/day in divided doses). It is a time-dependent antibiotic and can be used as both a monotherapy or in combination with other antibiotics (meropenem, colistin, amikacin, cefepime). Most clinical trials have been reported with ampicillin/sulbactam. Rifampicin in combination with colistin has also been shown to be beneficial in observational studies.[395-397] Although tigecycline is approved by the Food and Drug Administration (FDA) for the treatment of complicated intra-abdominal infections, complicated skin and soft tissue infections, and community-acquired bacterial pneumonia, emerging resistance of *Acinetobacter* spp. and limited therapeutic options have forced physicians to use tigecycline for off-label indications like HAP secondary to *Acinetobacter*. In recently published meta-analyses, tigecycline compared to other antibiotics has been associated with worse outcomes and even increased risk of death when used for treating patients with VAP.[398,399]

Recommendations:

1. For treatment of MDR *Acinetobacter* infections, we recommend the following drugs: carbapenems (1A), colistin (1A), sulbactam plus colistin (2B), sulbactam plus carbapenem (2B), and polymyxin B (2A).
2. Combination therapy with sulbactam and colistin or carbapenem for MDR *Acinetobacter* (in proven cases or suspected cases with multi-organ dysfunction syndrome) may be initiated. Sulbactam should be stopped after 5 days in patients responding to treatment (2B).

How to treat MDR Pseudomonas infections?

P. aeruginosa can be considered the prototype MDR Gram-negative bacilli causing hospital-acquired pneumonia (HAP) with at least five known mechanisms of resistance.[400]

The therapeutic options for MDR *Pseudomonas* include aminoglycosides (amikacin, tobramycin, netilmicin), β-lactam/β-lactamase inhibitors (piperacillin–tazobactam, cefoperazone–sulbactam, ticarcillin–clavulanate), antipseudomonal cephalosporins (cefepime, cefpirome), monobactam (aztreonam), fluoroquinolones (ciprofloxacin, levofloxacin), carbapenems (imipenem, meropenem), and polymyxins (colistin, polymyxin B). Carbapenems are the drugs of choice for *P. aeruginosa* that produce extended-spectrum β-lactamases. Adjunctive antibiotic therapy with inhaled antibiotics has been proposed in the management of MDR *Pseudomonas*; however, there is no clear evidence for its use.[400]

Recommendation

For treatment of MDR *Pseudomonas*, we recommend initial combination chemotherapy with a carbapenem and either a fluoroquinolone or an aminoglycoside (1A). Treatment should then be de-escalated to appropriate monotherapy.

OTHER ISSUES

What should be the strategy for prevention of VAP/HAP?

A detailed discussion on prevention of HAP/VAP is beyond the scope of these guidelines. We recommend the readers to refer other published documents for detailed discussion on prevention of HAP/VAP.[264,401-442] The strategies for prevention of VAP relevant to local conditions are listed in Table 18. The group re-emphasized staff education programs by hospital infection control committee and the concerned infection control nurse on a weekly basis (2A).

Table 18: Preventive strategies for VAP

The following strategies are recommended in prevention of VAP:
Oral cavity decontamination with 2% chlorhexidine (1A)[412-415]
Hand hygiene preferably using alcohol-based hand rubs or soap and water (1A)[416]
Use of sedation and weaning protocols (1A)[419,420]
Use of NIV to avoid intubation, where feasible (1A)[264,421]
Subglottic secretion drainage (2A)[422,423]
Heat moisture exchangers in place of heated humidifiers (2A)[424-428]
Closed suction systems (2A)[429-431]
Use of orotracheal intubation as opposed to nasotracheal intubation (2A)[432,433]
Proper and timely disposal of condensates (3A)[434,435]
Maintaining tracheal cuff pressures <25 cm H_2O (2A)[436]
Wipe stethoscopes with alcohol rubs (2A)[437]
Regular postural mobilization to prevent stasis of secretions (2A)
Use of only normal saline for suctioning (3A)
Proper sterilization of nebulizer and other chambers (2A)
Head end elevation to 30°–45° (2A)
The following strategies are not recommended in prevention of VAP:
Antibiotics for prevention of VAP (2A)
Selective digestive tract decontamination (2A)[438]
Routine ventilator circuit changes (2A)[439,440]
Early tracheostomy (2A)

What are the other good practices to be followed in the ICU?

Good practices are associated with improved ICU outcomes that need to be followed in ICUs. These include the following:

Stress ulcer prophylaxis

Stress ulcer prophylaxis should generally be avoided in order to preserve gastric function. Whenever stress ulcer prophylaxis is indicated, sucralfate should be preferred in order to reduce the risk of VAP. The two major risk factors for clinically important gastrointestinal bleeding due to stress ulceration include mechanical ventilation for >48 h and coagulopathy.[443] Proton pump inhibitors (PPI) are superior to H2 receptor antagonists (H2RA),[444] while H2RA are superior to antacids[445] or sucralfate.[446] Prophylactic agents that increase gastric pH (e.g. PPIs, H2RA, and antacids) may increase the risk of nosocomial pneumonia compared to agents that do not alter gastric pH (sucralfate).[447] In those with high risk of stress ulcer bleeding, H2RA and PPIs should be employed, with sucralfate reserved in patients with low to moderate risk of gastrointestinal bleeding.

Early enteral feeding

Enteral feeding is superior to parenteral nutrition and should be used whenever tolerated and in those without any contraindications to enteral feeding. Enteral nutrition is associated with a lower incidence of infection, but not mortality.[448]

Deep venous thrombosis prophylaxis

Pulmonary embolism remains the most common preventable cause of hospital death. DVT prophylaxis with unfractionated heparin (5000 U thrice a day) or a low-molecular-weight heparin should be routinely used in all ICU patients with no contraindications to prophylactic anticoagulation.[449]

Glucose control

We recommend a plasma glucose target of 140–180 mg/dL in most patients with pneumonia, rather than a more stringent target (80–110 mg/dL) or a more liberal target (180–200 mg/dL). This glucose range avoids hyperglycemia, while minimizing the risk of both hypoglycemia and other harms associated with a lower blood glucose target.[450]

Blood products

Red blood cells should be transfused at a hemoglobin threshold of <7 g/dL except in those with myocardial ischemia and pregnancy.[451] Platelet transfusion is indicated in patients with platelet count <10,000/μL, or <20,000/μL if there is active bleeding. Fresh frozen plasma is indicated only if there is a documented abnormality in the coagulation tests and there is active bleeding or if a procedure is planned.

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