

The diagnosis and management of hospital acquired pneumonia, ventilator-associated pneumonia and healthcare-associated pneumonia

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Hospital acquired pneumonia (HAP), ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia (HCAP) remain important causes of morbidity and mortality despite advances in antimicrobial therapy, supportive care and preventive measures. HAP is defined as a pneumonia that is not incubating at the time of hospital admission and begins 48 hours or more after admission. VAP is a pneumonia occurring more than 48-72 hours after endotracheal intubation. HCAP refers to pneumonia in a patient who was in an acute care hospital for 2 or more days in the preceding 90 days; resided in a nursing home or a long-term care facility; within the past 30 days received intravenous antibiotics, chemotherapy, wound care or attended a hospital or haemodialysis clinic¹.

Epidemiology

HAP is the second most common nosocomial infection in the USA and is associated with a high morbidity and mortality^{1,2}. The attributable mortality of HAP is estimated to be 27-50%. It is the most common infection in the intensive care units (ICU) with an incidence ranging from 6-52%. Mechanical ventilation increases the risk of HAP by 6-20 fold³. The incidence is the highest in mechanically ventilated patients with ARDS⁴.

Aetiology

HAP, VAP and HCAP are usually caused by aerobic Gram-negative bacteria (e.g. *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Acinetobacter* species). Multi drug resistant (MDR) pathogens are commonly involved with *P. aeruginosa* being the most common. Pneumonia due to *Staphylococcus aureus* (mostly methicillin resistant *S. aureus* -MRSA) is more common in patients with diabetes mellitus, head trauma and those in ICUs. *Sterptococcus pneumoniae* and *Haemophilus influenzae* cause early onset HAP in patients without other risk factors. Anaerobes are an uncommon cause

of VAP. Infection with *Legionella pneumophila* occurs at considerably varying rates among hospitals. Virus and fungal infections are unusual in immunocompetent patients with HAP and VAP^{3,4,5}.

Time of onset of pneumonia is an important determinant of specific pathogens and outcomes. Early onset HAP and VAP (occurring within the first 4 days of hospitalisation) are more likely to be caused by antibiotic sensitive bacteria and carry a better prognosis. Late onset HAP and VAP (occurring after 5 days or more) are usually due to MDR pathogens and have a high morbidity and mortality. However, other factors may increase the risk of MDR pathogens in early onset pneumonias^{3,4}. (Table 1)

Table 1. Risk factors for MDR pathogens causing HAP, VAP and HCAP¹

- Antimicrobial therapy in preceding 90 days
- Current hospitalisations of 5 days or more
- High frequency of antibiotic resistance in the community/ hospital unit
- Presence of risk factors for HCAP
 - Hospitalisation for 2 or more days in the preceding 90 days
 - Resident in a nursing home/ extended care facility
 - Home infusion therapy (including antibiotics)
 - Chronic dialysis within 30 days
 - Home wound care
 - Family member with MDR pathogen
- Immunosuppressive disease/ therapy

Pathogenesis

For HAP to occur, the micro organisms should be able to overcome the host defences, which usually prevent their invasion and colonisation. A number of host and treatment-related colonization factors, such as the severity of the patient's underlying disease, prior surgery, exposure to antibiotics or other medications, and the use of invasive respiratory devices, are important in the pathogenesis of HAP and VAP^{6,7}. Healthcare devices, the environment (air, water, equipment, and fomites) and infected staff or other patients, all act as sources of pathogens for HAP.

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Aspiration of oropharyngeal secretions and leakage of bacteria around the endotracheal tube cuff, and the primary routes of bacterial entry into the lower respiratory tract. Haematogenous spread, inhalation of microorganisms and bacterial translocation from the gastrointestinal tract lumen are uncommon pathogenic mechanisms. The stomach and sinuses may be potential reservoirs for pathogens, but their contribution to HAP is controversial^{8,9,10}.

Risk factors and risk factor modification

General risk factors for developing HAP include, age over 70 years, male sex, serious co-morbidities, malnutrition, impaired consciousness, intubation and mechanical ventilation, prolonged hospitalisation, and pre-existing pulmonary disease^{4,11}. It is important to target the modifiable risk factors for prophylaxis and improved management in HAP. Effective strategies include; strict infection control, use of microbiologic surveillance, minimizing intubation and ventilation, proper positioning, and optimal patient management to reduce the duration of ICU stay.^{1,12} (Table 2)

Diagnosis

The goals of diagnostic approaches in patients with suspected HAP are to identify the patients with pulmonary infection; to ensure collection of appropriate cultures; to promote the use of early, effective antibiotic therapy with de-escalation when possible; and to identify patients who have extrapulmonary infection¹.

The best diagnostic strategy in patients with suspected VAP remains contentious^{1,5}. The central problem is the difficulty in striking a balance between avoiding a delay in starting antibiotics when required and reducing the inappropriate use of broad-spectrum antibiotics. Delay in initiating antibiotics leads to excess mortality in VAP, while overuse of antibiotics is a major factor in the increase in multiantibiotic-resistant pathogens.

Two different strategies are available for diagnosis; a clinical strategy and a bacteriologic strategy. Each strategy has its own advantages and disadvantages^{1,13}.

Table 2. Recommendations for risk factor modification¹

General prophylaxis

- Effective infection control measures to reduce cross-infection with MDR pathogens. (staff education, alcohol-based hand disinfection & isolation)
- Surveillance of ICU infections, identify and quantify endemic and new MDR pathogens and guide appropriate antimicrobial therapy in patients with suspected HAP or other nosocomial infection

Intubation and mechanical ventilation

- Avoid intubation and reintubation if possible and reduce the duration of intubation and mechanical ventilation to a minimum. Noninvasive ventilation should be used whenever possible.
- Orotracheal intubation and orogastric tubes are preferred over nasotracheal intubation and nasogastric tubes to prevent nosocomial sinusitis.
- Continuous aspiration of subglottic secretions can reduce the risk of early-onset VAP.
- The endotracheal tube cuff pressure should be maintained at > 20cmH₂O to prevent leakage of bacterial pathogens around the cuff.
- Contaminated condensate should be carefully emptied from ventilator circuits and condensate should be prevented from entering either the endotracheal tube or inline medication nebulizers.

Aspiration, body position, and enteral feeding

- Patients should be kept in the semi recumbent position (30°-45°) rather than supine to prevent aspiration, especially when receiving enteral feeding.
- Enteral nutrition is preferred over parenteral nutrition to reduce the risk of complications related to central intravenous catheters and to prevent reflux villous atrophy of the intestinal mucosa that may increase the risk of bacterial translocation.

Modulation of colonization: oral antiseptics and antibiotics

- Prophylactic oral or systemic antibiotics especially at intubation and the use of oral chlorhexidine have prevented HAP in some studies - but are not recommended for routine use.
- Use daily interruption or lightening of sedation to avoid constant heavy sedation and try to avoid paralytic agents, both of which can depress cough and thereby increase the risk of HAP.

Transfusion and hyperglycemia

- Transfusion of red blood cell and other allogeneic blood products should follow a restricted transfusion trigger policy; leukocyte-depleted red blood cell transfusions can help to reduce HAP in selected patient populations
- Intensive insulin therapy is recommended to maintain serum glucose levels between 80 and 110 mg/dl in ICU patients to reduce nosocomial blood stream infections, duration of mechanical ventilation, ICU stay, morbidity, and mortality.

Clinical strategy

When the clinical approach is used, pneumonia is defined by the presence of a new or progressive chest radiographic infiltrate plus at least two of three clinical features suggestive of infection (fever > 38°C, leukocytosis or leukopenia, purulent secretions)¹. The aetiology is defined by semiquantitative cultures of endotracheal aspirates or sputum microscopy.

Semiquantitative cultures may not reliably separate true pathogens from colonizers and a non-infectious process (e.g. heart failure, atelectasis, pulmonary thromboembolism, pulmonary drug reactions, pulmonary haemorrhage, ARDS) may be responsible for the clinical findings^{13,14}. Therefore the major limitations of this approach are that it is overly sensitive and leads to more antibiotic therapy than when using the bacteriologic strategy¹⁵.

Bacteriologic strategy

The bacteriologic strategy uses quantitative cultures of lower respiratory secretions to define both the presence of pneumonia and the aetiological pathogen¹. Quantitative cultures can be performed on bronchoscopic (invasive) or nonbronchoscopic (non-invasive) samples (i.e. endotracheal aspirates, bronchoalveolar lavage or protected specimen brush samples)^{16,17}. Bronchoscopy may not be freely available in all instances, but bronchoscopic and non-bronchoscopic samples have shown no significant difference in the diagnostic yield¹. Each technique has its own diagnostic threshold and methodologic limitations. The choice of method depends on local expertise, experience, availability, and cost^{17,18}.

This approach tries to separate colonizers from pathogens and has consistently led to finding fewer microorganisms above the diagnostic threshold than in qualitative cultures. It also treats less patients with antibiotics, and uses a potentially narrower spectrum of therapy than when using the clinical strategy¹⁷.

The major concerns here are that a false negative culture can lead to a failure to treat either a specific patient or a specific pathogen, and that the results are not always consistent or reproducible. A recent starting of or change in antibiotics (especially in the preceding 24 hours, but up to 72 hours) can lead to a false negative result. Some patients, especially those with early pneumonia, will have culture growth below threshold even without recent antibiotic changes.

An algorithm for the diagnosis and management of HAP has therefore been compiled, by the

combination of the clinical and bacteriologic strategies (Figure 1).

What should be done when a patient is suspected to have HAP?

When HAP is suspected clinically (fever > 38°C, leukocytosis or leukopenia, purulent secretions), the patient should have a chest radiograph, and if it shows new or progressive infiltrates or an air bronchogram sign, lower respiratory tract secretions should be obtained for culture^{1,15}.

- The chest radiograph should preferably be posteroanterior and lateral, as portable x-rays have limited accuracy. This can also assist in defining the severity (multilobar or not) and recognising complications (effusions and cavitations).
- Samples of lower respiratory tract should be obtained before commencing or changing antibiotics. bronchoscopic or non-bronchoscopic methods could be used to collect the samples. LRT cultures have a high negative predictive value and thus a sterile culture in the absence of new antibiotics in the preceding 72 hours virtually excludes bacterial pneumonia, though viral or Legionella pneumonia is still possible^{5,18}.
- All patients with suspected VAP should also have their arterial oxygenation measured and blood cultures obtained, though blood cultures have very low sensitivity to diagnose VAP¹⁹.

When should suspected HAP be treated?

The presence of a new or progressive radiographic infiltrate plus at least two of three clinical criteria (fever > 38°C, leukocytosis or leukopenia, purulent secretions) give the most accurate combination of criteria for commencing empiric antibiotic therapy^{20,21}. When fever, leukocytosis, purulent sputum and a positive culture of sputum or tracheal aspirate are present without a new lung infiltrate, nosocomial tracheobronchitis should be considered²².

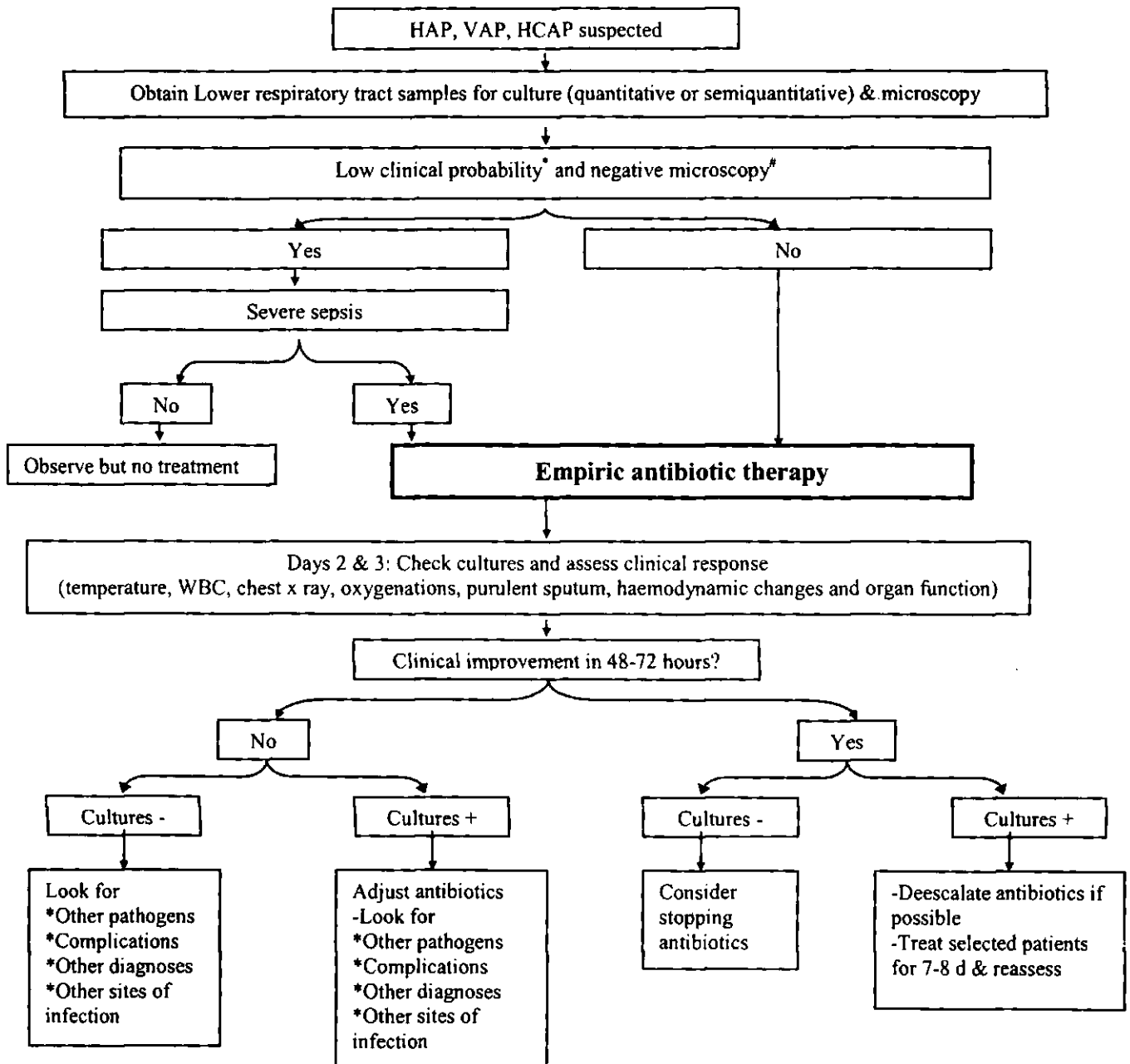
In patients with ARDS, it may be difficult to demonstrate new or progressive radiographic infiltrates. Thus the presence of at least one clinical criterion or other features such as haemodynamic instability or deterioration in blood gases should warrant more diagnostic testing²³.

Management

If a patient is suspected to have HAP, prompt, appropriate and adequate empiric antibiotic therapy needs to be commenced, as delays in initiating antibiotics have led to increased mortality in

VAP^{24,25,26}. However, the need for de-escalation of antibiotics according to clinical response and microbiological data has to be kept in mind^{20,27}. (Figure 1)

Figure 1. Summary of the management strategies for patients with HAP, VAP and HCAP



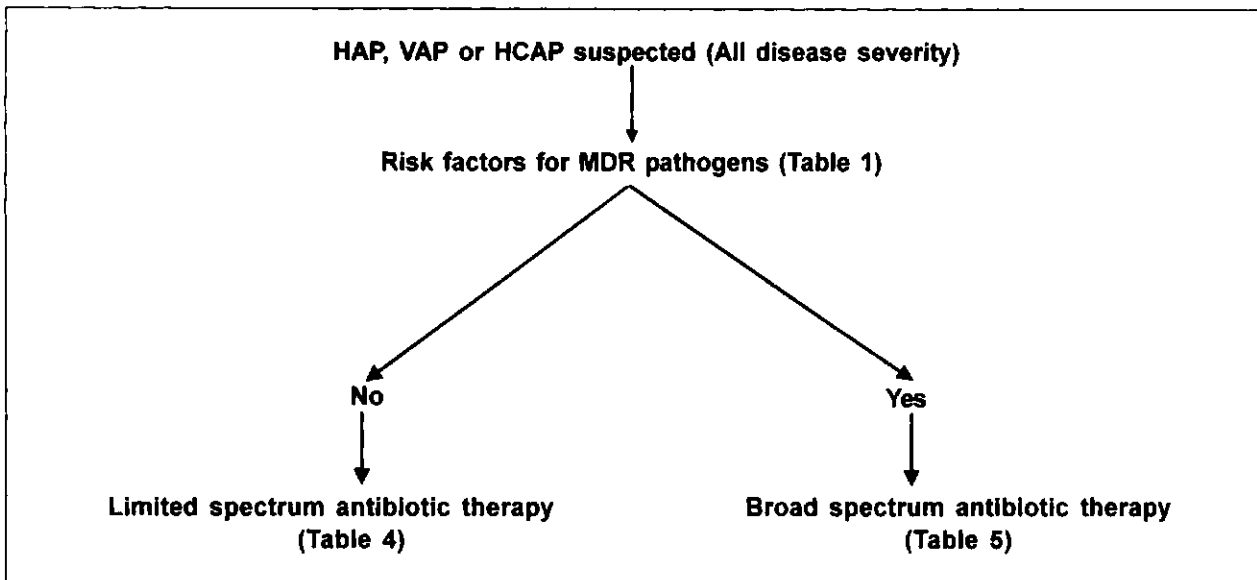
* A low clinical probability is when the patient does not have the presence of a new or progressive radiographic infiltrate plus at least two of three clinical criteria (fever > 38°C, leukocytosis or leukopaenia, purulent secretions).

Negative microscopy is the absence of bacteria or inflammatory cells in the tracheal aspirate.

Antibiotic therapy

The key factor in deciding initial empiric antibiotic therapy is the presence or absence of risk factors for MDR organisms^{1,4} (Figure 2). An adequate therapy regimen should also have the optimal dose, the correct route of administration, and the use of combination therapy when necessary. Initial therapy should be administered intravenously and switched to oral/ enteral therapy in those with a good clinical response and a functioning intestinal tract. Though the guidelines recommend antibiotic regimens, the choice of specific antibiotic should be guided by local microbiological data, cost, availability and formulary restrictions^{4,28}.

Figure 2. Algorithm for initiating empiric antibiotic therapy for HAP, VAP & HCAP¹



Combination therapy should be used in patients with risk factors for infection with MDR organisms (especially if *P. aeruginosa* is documented)^{1,28}. Monotherapy with selected antibiotics can be used for patients with HAP and VAP in the absence of resistant pathogens^{2,28}. However, they should receive combination therapy until the lower respiratory tract cultures confirm that a single agent can be used^{1,5}. (Tables 5, 6, 7 & 8).

Antibiotic restriction can limit epidemics of infection with specific resistant pathogens. Heterogeneity of antibiotic prescriptions, including formal antibiotic cycling, may be able to reduce the overall frequency of antibiotic resistance¹.

In those with a good clinical response, the duration of therapy could be shortened to periods as short as 7 days (from the traditional 14-21 days) if the pathogen is not *Pseudomonas aeruginosa*^{3,20}.

Table 4. Initial empiric antibiotic therapy for HAP or VAP in patients with no known risk factors for MDR pathogens¹.

Potential pathogen	Recommended antibiotic
<i>Streptococcus pneumoniae</i> [†]	Ceftriaxone
<i>Haemophilus influenzae</i>	or
Methicillin-sensitive <i>Staphylococcus aureus</i>	Levofloxacin, moxifloxacin, or ciprofloxacin
Antibiotic-sensitive enteric Gram-negative bacilli	or
<i>Escherichia coli</i>	Ampicillin/sulbactam
<i>Klebsiella pneumoniae</i>	or
<i>Enterobacter</i> species	Ertapenem
<i>Proteus</i> species	
<i>Serratia marcescens</i>	

[†] The frequency of penicillin-resistant *S. pneumoniae* and multidrug-resistant *S. pneumoniae* is increasing; levofloxacin or moxifloxacin are preferred to ciprofloxacin and the role of other new quinolones, such as gatifloxacin, has not been established.

Table 5. Initial empiric antibiotic therapy for HAP, VAP & HCAP in patients with risk factors for MDR pathogens¹

Potential pathogens	Combination antibiotic therapy ⁺
Pathogens listed in Table 4 and MDR pathogens <i>Pseudomonas aeruginosa</i> <i>Klebsiella pneumoniae</i> (ESBL) [†] <i>Acinetobacter</i> species [†] <i>Legionella pneumophila</i> [*]	Antipseudomonal cephalosporin (cefepime, ceftazidime) <i>or</i> Antipseudomonal carbapenem (imipenem or meropenem) <i>or</i> β -Lactam/ β -lactamase inhibitor (piperacillin-tazobactam) <i>plus</i> Antipseudomonal fluoroquinolone [‡] (ciprofloxacin or levofloxacin) <i>or</i> **Aminoglycoside (amikacin, gentamicin, or tobramycin) <i>plus</i>
Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	***Linezolid or vancomycin

[†] If an ESBL (Extended spectrum β lactamase) strain, such as *K. pneumoniae*, or an *Acinetobacter* species is suspected, a carbapenem is a reliable choice.

^{*} If *L. pneumophila* is suspected the combination antibiotic regimen should include a macrolide (e.g. azithromycin) or a fluoroquinolone (e.g. ciprofloxacin or levofloxacin) should be used rather than an aminoglycoside.

** Aminoglycoside can be stopped after 5-7 days in responding patients.

*** If MRSA risk factors are present or there is a high incidence locally.

Table 6. Initial intravenous adult doses of antibiotics for empiric therapy of HAP, VAP and HCAP in patients with risk factors for MDR pathogens¹

Antibiotic	Dosage [*]
Antipseudomonal cephalosporin	
Cefepime	1-2 g every 8-12 h
Ceftazidime	2 g every 8 h
Carbapenems	
Imipenem	500 mg every 6 h or 1 g every 8 h
Meropenem	1 g every 8 h
β -Lactam/ β -lactamase inhibitor	
Piperacillin-tazobactam	4.5 g every 6 h
Aminoglycosides	
Gentamicin	7 mg/kg per d [†]
Tobramycin	7 mg/kg per d [†]
Amikacin	20 mg/kg per d [†]
Antipseudomonal quinolones	
Levofloxacin	750 mg every d
Ciprofloxacin	400 mg every 8 h
Vancomycin	15 mg/kg every 12 h [‡]
Linezolid	600 mg every 12 h

^{*} Dosages are based on normal renal and hepatic function.

[†] Trough levels for gentamicin and tobramycin should be less than 1 μ g/ml, and for amikacin they should be less than 4-5 μ g/ml.

[‡] Trough levels for vancomycin should be 15-20 μ g/ml.

Table 7. Specific antibiotic regimens¹

<i>Acinetobacter</i> Spp	<ul style="list-style-type: none"> - Most active agents are carbapenams, sulbactam, colistin, and polymyxin - Colistin for carbapenam resistant <i>Acinetobacter</i> spp
EBSL+ Enterobacteraeae	<ul style="list-style-type: none"> - Most active agents are carbapenams - Avoid monotherapy with a third generation cephalosporin
MDR Gram-negative pneumonia with poor response	<ul style="list-style-type: none"> - Consider adding inhaled polymyxin or aminoglycoside

Response to therapy

Resolution of HAP can be defined either clinically or microbiologically. Clinical improvement usually becomes apparent after 48-72 hours of therapy. Thus the selected antibiotic regimen should not be changed during this period unless progressive deterioration is noted or initial culture results suggest a change in the antibiotic regimen¹. The responding patient should have de-escalation of antibiotics, narrowing the regimen according to the most appropriate antibiotic defined by the culture results²⁸.

Lower respiratory tract cultures can be used to define microbiologic resolutions. Chest radiographs however have a limited value in defining resolution, as radiographic improvement often lags behind clinical response, especially in the elderly and those with co-morbidities (e.g. COPD)²⁹. However a rapidly deteriorating chest x ray progressing to multilobar involvement, a greater than 50% increase in the size of the infiltrate in less than 48 hours, cavitation or significant pleural effusion needs further evaluation²⁰.

Evaluation of non-responders

An aggressive evaluation is necessary for those who are deteriorating on initial therapy. It may be necessary to broaden the antibiotic coverage while awaiting culture results. The non-responding patient should be evaluated for complications of pneumonia, unsuspected or resistant organisms, extra pulmonary infection or non-infectious mimics of pneumonia³⁰ (Table 8).

Table 8. Reasons for poor response

1. Host factors
 - a. Prolonged mechanical ventilation
 - b. Age > 60 years
 - c. Bilateral radiographic infiltrates
 - d. Prior antibiotic therapy
 - e. Prior pneumonia/ chronic lung disease
2. Bacterial
 - a. Drug resistant pathogen (bacteria, mycobacteria, virus, fungus)
 - b. Inadequate antimicrobial therapy
3. Complications
 - a. Empyema/ lung abscess
 - b. *Clostridium difficile* colitis
 - c. Occult infection
 - d. Drug fever
4. Incorrect diagnosis
 - a. Atelectasis
 - b. Pulmonary embolus
 - c. ARDS
 - d. Pulmonary haemorrhage
 - e. Underlying disease
 - f. Neoplasm

If the non-responding patient remains haemodynamically stable, and evaluations including radiography and bronchoscopy are unrevealing, a change in antibiotics or addition of corticosteroids may be appropriate before proceeding with an open biopsy. However, those showing early deterioration (within 48-72 hours of commencing therapy) or have initial improvement followed by deterioration, the addition of antibiotics against resistant or unusual organisms can be done while continuing with aggressive evaluation¹.

Key points

- HAP, VAP and HCAP are treated on similar principles.
- Preventive strategies should be applied to modifiable risk factors.
- Diagnosis is based on history, examination, chest radiography and culture of lower respiratory tract secretions. Lower respiratory tract cultures should be obtained prior to commencing or changing antibiotics.
- **Early, appropriate and adequate empiric antibiotic therapy is the key factor in the management**, as delays in initiating antibiotics have led to increased mortality in VAP. (Do not wait for microbiological confirmation to commence antibiotics.)
- The antibiotic regimen depends on the presence or absence of risk factors for MDR organisms and not on the severity of pneumonia.
- De-escalation of antibiotics can be done after 48-72 hours in responding patients, provided the organism cultured is not *Pseudomonas aureginosa*.
- The duration of treatment could be shortened to 7-8 days in those with a good clinical response if not infected by *P. aureginosa*.
- Aggressive evaluation needs to be done in non-responders, looking for complications, resistant or unusual pathogens, extrapulmonary sites of infection and non infectious mimics of pneumonia.

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Questions

Question 1

A young woman with Guillain Barre Syndrome was admitted to the ICU as she required mechanical ventilation. She had been previously healthy.

Which of the following will be the best method of preventing her developing ventilator-associated pneumonia?

- A. Commencing non-invasive ventilation instead of invasive ventilation.
- B. Nursing in semi recumbent position.
- C. Commencing on prophylactic broad-spectrum antibiotics at the time of endotracheal intubation.
- D. Arranging parenteral nutrition instead of orogastric feeding.
- E. Performing daily cultures of tracheal aspirate.

Question 2

A 60-year-old lady sustained a fracture neck of femur after a fall. She had been in good health and living with her daughter. Four days after hospitalization, she developed fever and a productive cough. Her chest radiograph revealed an early consolidation. She was suspected to have hospital acquired pneumonia and appropriate investigations were performed.

(i) Which is the most likely causative organism for the pneumonia in this lady?

- A. *Streptococcus pneumoniae*
- B. *Methicillin Resistant Staphylococcus aureus*
- C. *Pseudomonas aeruginosa*
- D. *Anaerobic bacteria*
- E. *Legionella pneumophilla*

(ii) The best empiric intravenous antibiotic regimen to treat her would be

- A. clarythromycin monotherapy
- B. ciprofloxacin monotherapy
- C. cefuroxime + meropenam
- D. amoxicillin + vancomycin
- E. ceftriaxone + gentamicin

(iii) 48 hours after commencing the initial empiric antibiotic therapy, she still had high fever but was haemodynamically stable. Her sputum culture revealed no growth. Which of the following is the most appropriate in this situation?

- A. Stop antibiotics and observe for 24-48 hours.
- B. Add on anti-tuberculosis treatment.
- C. Add a short course of high-dose steroids.
- D. Arrange further investigations for the cause of fever.
- E. Plan for urgent CT guided biopsy of the consolidation.