

Hospital-acquired pneumonia

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Summary

Hospital-acquired (nosocomial) pneumonia (HAP) is the second most common hospital-acquired infection, with an incidence of 5-15 per 1000 hospital admissions. The incidence is higher in Intensive Care Units, where it accounts for approximately 30% of all hospital-acquired infections and is accompanied by significant morbidity and mortality. It is particularly associated with mechanical ventilation, where it prolongs the duration of mechanical ventilation required and the length of ICU stay. Mortality in patients with HAP ranges from 20-50%. This is increased to approximately 75% in cases caused by multi-drug resistant organisms.

DEFINITIONS AND CAUSATIVE ORGANISMS

Pneumonia is an inflammatory condition of the lungs secondary to bacterial, viral or fungal infection. Pathogens are most commonly acquired in the community, prior to admission to hospital.

Hospital-acquired pneumonia (HAP) is defined as pneumonia occurring more than 48 hours after hospital admission.

Ventilator-associated pneumonia (VAP) is a specific sub-group of HAP, occurring in patients more than 48 hours after endotracheal intubation and initiation of mechanical ventilation.

HAP can be further classified as early or late onset, which can be useful in predicting the likely causative organisms and choosing appropriate antibiotics. Early onset HAP occurs within 5 days of admission to hospital and is more likely to be caused by community-acquired pathogens such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Such pathogens are usually susceptible to antibiotic therapy. Late onset HAP develops more than five days after admission and is more likely to be caused by opportunistic and drug-resistant organisms such as *Pseudomonas aeruginosa* and *meticillin-resistant Staphylococcus aureus* (MRSA). There has been a recent increase in the number of early onset HAPs caused by the more drug-resistant organisms

such as MRSA. Such patients have usually had a recent hospital admission (within the previous 90 days) or are resident in nursing homes. It is also more common in patients who attend hospital frequently, for example, for haemodialysis.

The most common causative organisms are outlined in Table 1. Polymicrobial infections occur in up to 60% of cases. Anaerobic infections are rare. Fungal infections can occur, most often in severely immunocompromised patients.

PATHOGENESIS AND RISK FACTORS

For pneumonia to develop, there must be colonisation of the lower respiratory tract with the offending pathogen. Development of pneumonia following colonisation then depends on the balance between host defences and the virulence and volume of pathogen present in the lungs.

In VAP, colonisation usually occurs by micro-aspiration from the oropharynx or the gastrointestinal tract, often due to leakage around a cuffed endotracheal tube. Colonisation of the tube itself and condensation in the ventilator circuit can also contribute. Macro-aspiration from the gastrointestinal tract will result in the direct inoculation of a large volume of pathogen into the lower airway. Haematogenous spread from a distant site of infection can also occur, but is rare in cases of HAP.

Table 1. Causative organisms in HAP/VAP.

Pathogen	Examples
Staphylococcus aureus	Meticillin-sensitive (MSSA) or meticillin-resistant (MRSA)
Enterobacteriaceae	Klebsiella, Escherichia coli, Proteus, Enterobacter, Serratia
Streptococcus spp.	Streptococcus pneumoniae
Haemophilus spp.	Haemophilus influenzae
Pseudomonas aeruginosa	
Acinetobacter spp.	
Neisseria spp.	
Others	Stenotropomonas, Moraxella, Enterococcus, Corynebacterium, anaerobes, fungi

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Bearing this in mind, the most significant risk factor for the development of HAP in ICU is therefore tracheal intubation and mechanical ventilation. Other risk factors include:

- **Patient factors**

Advanced age, immunosuppression, severe acute illness, co-existing chronic illness - particularly chronic lung disease, malnutrition.

- **Factors that enhance colonisation of the oropharynx and stomach**

Recent antibiotic therapy, gastric acid suppression, bolus enteral feeding, prolonged or recent hospital admission, poor oral hygiene.

- **Conditions predisposing to aspiration or reflux**

Tracheal intubation (especially frequent re-intubations), insertion of nasogastric tube, supine positioning, coma, paralysis.

- **Prolonged periods of mechanical ventilation**

Particularly with the development of ARDS.

DIAGNOSIS

The diagnosis of HAP can be difficult, as the clinical features can be non-specific and the patient may already be unwell from other causes, resulting in a mixed clinical picture. Infiltrates on the chest Xray can also occur due to a number of other disease processes, such as ARDS, cardiogenic pulmonary oedema and atelectasis or collapse of lung segments or lobes.

There are no universally accepted clinical criteria for the diagnosis of HAP. The American Thoracic Society suggests that the diagnosis should be considered in any patient with new or progressive radiological infiltrates and clinical features to suggest infection:¹

- Fever (core temperature $>38^{\circ}\text{C}$),
- Leukocytosis ($>10000\text{mm}^{-3}$) or leukopenia ($<4000\text{mm}^{-3}$),
- Purulent tracheal secretions,
- Increased oxygen requirements, reflecting new or worsening hypoxaemia.

There is little evidence to support the use of more advanced radiological imaging although, when available, computed tomography can be useful in certain cases to exclude other pathology.

While clinical, laboratory and radiological examinations may raise the suspicion of HAP, determining the microbiological cause is more difficult and relies on obtaining a positive culture from the lower respiratory tract. Samples can be obtained from expectorated sputum in non-intubated patients, endotracheal aspirates (ETA), broncho-alveolar lavage using a fiberoptic scope (BAL), and protected specimen brush (PSB) sampling. Sputum and ETAs are the easiest samples to obtain and are highly sensitive with a high negative predictive value. A negative sample will essentially exclude HAP from the differential diagnosis. However, colonising organisms from the lower or upper respiratory tract often contaminate the sample, making it difficult to distinguish these from the causative pathogen. Samples obtained by BAL or brushings are more specific, however this is more invasive and requires bronchoscopic guidance.

False negative results can also occur, due to taking the sample too early in the disease process (when bacterial load is low), sampling an unaffected segment of lung, or sampling after starting antibiotic therapy.

Taking these factors into account, recent UK guidelines recommend that the least invasive, least expensive and most readily available technique in the clinical setting is satisfactory.² Samples taken before antibiotics are given are more likely to yield a positive result, however, collection of samples should not delay commencing appropriate antibiotic therapy in critically ill patients.

PREVENTATIVE MEASURES

The majority of hospital-acquired infections are preventable by reducing the risk factors associated with their development and paying attention to basic infection control procedures. There is now good evidence supporting basic hand hygiene measures as a means of preventing disease transmission.^{2,3} However, there is a lack of robust evidence supporting many of the other recommended practices.

Recommendations come from the American Thoracic Society (US)¹ and the National Institute of Clinical Excellence (UK)³. One of the most important strategies involves delivery of preventative measures as part of a care bundle with appropriate education and training of all healthcare workers in its delivery. This has been shown to be a cost effective way of improving compliance with preventive measures.

Components of such a care bundle should include:

Prevention of transmission of microorganisms

- Good hand hygiene measures and wear gloves for contact with patient or contaminated secretions,
- No routine changing of ventilator circuits/heat and moisture exchangers unless specifically indicated (malfunction or visible contamination).

Prevention of aspiration related to endotracheal intubation

- Early weaning and daily sedation breaks to reduce the duration of endotracheal intubation and mechanical ventilation as much as possible,
- Avoidance of repeated re-intubations,
- Control of endotracheal cuff pressures between 20-30cmH₂O,
- Use of endotracheal tubes with sub-glottic drainage ports,
- Use of non-invasive ventilation if clinically appropriate.

Prevention of aspiration associated with enteral feeding

- Semi-recumbent positioning (30-45° head up) if possible,
- Confirm correct placement of nasogastric tube prior to use.

Prevention of oropharyngeal colonisation

- Oral hygiene strategy for patients at risk of HAP, including the use of an oral anti-septic agent e.g. chlorhexidine gel.

Selective decontamination of the digestive tract (SDD) involves the use of local and systemic antibiotics to prevent colonisation

of the gastrointestinal (GI) tract with gram-negative bacteria and yeasts, whilst maintaining normal levels of anaerobic flora. Specific regimes vary but most involve the oral administration of a non-absorbable aminoglycoside/anti-fungal, combined with an intravenous cephalosporin. A recent Cochrane review found that SDD was associated with a reduction in both the incidence of HAP and overall mortality.⁴ However, it remains controversial and is not used routinely in the UK, due to concerns over the emergence of drug-resistant bacteria and an increase in the rate of *Clostridium difficile* infections (pseudomembranous colitis).³

TREATMENT – CHOICE AND DURATION OF ANTIBIOTIC THERAPY

The general approach to the treatment of HAP involves prompt initiation of a broad-spectrum empirical antibiotic regime. Minimising any delay between recognition of HAP and initiation of treatment will improve prognosis and reduce length of stay and associated costs. After 48-72 hours, this is followed by de-escalation to a narrower spectrum of cover, guided by culture results.

Empirical antibiotics

The initial choice of empirical antibiotics depends on three factors:

- Timing of onset from admission to hospital (early or late),
- Risk factors for multi-drug resistant organisms,
- Knowledge of local pathogens and patterns of resistance.

In patients with early onset HAP, without risk factors for resistant organisms, antibiotic therapy should cover community-acquired pathogens and non-resistant gram-negative Enterobacteriaceae. For

late-onset HAP or for any patient with risk factors for multi-drug resistant (MDR) pathogens, empirical therapy should be broadened to cover MRSA and other resistant organisms.

Knowledge of local pathogens and patterns of resistance is essential as the most common reason for treatment failure is inadequate initial coverage, leading to further broadening of antibiotic coverage. Not only is this associated with poorer patient outcomes; it also increases the risk of new resistance patterns developing. De-escalation to a narrower spectrum, and preferably single, agent based on culture results, is also important in reducing the development of resistant pathogens.

Antibiotics should be administered intravenously and only stepped down to oral administration in patients with a good clinical response and a functioning GI tract. Aerosolised antibiotics have not been shown to be of any benefit in HAP.^{1,2}

Examples of specific regimes are detailed in Table 2.

DURATION OF ANTIBIOTIC THERAPY

The optimal duration of antibiotic therapy required in HAP is unknown. A large, multi-centre randomised control trial reported similar outcomes in patients with non-MDR organisms treated for 8 days and 15 days.⁵ Patients with MDR pathogens in the 8-day group were more likely to develop a recurrent infection than those in the 15-day group.

In general, 7-10 days is considered a suitable duration for patients with sensitive organisms. Those with resistant organisms may require 14-21 days of therapy. Clinical parameters such as improvement in

Table 2. Suggested empirical antibiotic regimes - MDR = multi-drug resistant.

Onset	Empirical antibiotic therapy	Example
Early onset	2nd/3rd generation cephalosporin or β-lactam/β-lactamase inhibitor or fluoroquinolone	cefuroxime/ceftriaxone amoxicillin + clavulanic acid ciprofloxacin/levofloxacin
Late onset or Risk factors for MDR pathogen	anti-pseudomonal cephalosporin or anti-pseudomonal carbapenam or broad spectrum β-lactam/β-lactamase inhibitor and either aminoglycoside or fluoroquinolone If MRSA suspected glycopeptide or oxazolidinone	ceftazidime meropenem piperacillin + tazobactam (Tazocin) gentamicin ciprofloxacin/levofloxacin vancomycin linezolid
	<i>Linezolid may have better tissue penetration than vancomycin in VAP</i>	

Table 3. Clinical Pulmonary Infection Score (CPIS).

Points	0	1	2
Tracheal secretions	Minimal	Abundant	Purulent
Chest Xray	No infiltrates	Diffuse infiltrates	Localised infiltrates
Temperature (°C)	36.5-38.4	38.5-38.9	≥39 or ≤36
Leukocytes (mm ⁻³)	4000-11000	<4000 or >11000	<4000 or >11000 plus band forms >500
PaO ₂ /FiO ₂ ratio (mmHg)	>240 or ARDS		<240 and no ARDS
Microbiology	Negative		Positive

oxygenation, white cell count and resolution of fever are more reliable in determining response to antibiotics and resolution of infection, than radiographic or microbiological parameters.

The Clinical Pulmonary Infection Score (CPIS) was originally designed as a tool to aid diagnosis of HAP but has been shown to have poor sensitivity and specificity in this role.⁶ However, a modified version can be used as a surrogate measure of response to antibiotic therapy (Table 3). A baseline score of ≥6 is indicative of HAP. Clinical improvement takes at least 48-72 hours. A falling score on day 3 indicates a response to treatment and can help identify patients who may be suitable to receive shorter courses of antibiotics. Of all the components of CPIS, an improvement in arterial oxygenation indicated by the PaO₂/FiO₂ ratio is the most valuable factor in predicting response to treatment.

CONCLUSION

Hospital-acquired pneumonia, in particular ventilator-associated pneumonia, is one of the most common complications associated with intensive care. It significantly contributes to morbidity and mortality, as well as increasing length of hospital stay and overall healthcare costs. Delivering a care bundle of simple preventive measures and ensuring timely initiation of appropriate antibiotics will help ensure better outcomes for patients with HAP.

REFERENCES

1. American Thoracic Society. Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia. *Am J Respir Crit Care Med* 2005; **171**: 388-416.
2. Masterton RG, Galloway A, French G, Street M, Armstrong J et al. Guidelines for the management of hospital-acquired pneumonia in the UK. *J Antimicrob Chemot* 2008; **62**: 5-34.
3. National Institute for Health and Clinical Excellence (NICE), National Patient Safety Agency (NPSA). Technical patient safety solutions for ventilator-associated pneumonia in adults. August 2008, Ref: NICE/NPSA/2008/PSG002. Available at: <http://guidance.nice.org.uk/PSG002/Guidance/pdf/English>
4. Liberati A, D'Amico R, Pifferi S, Torri V, Brazzi L, Parmelli E. Antibiotic prophylaxis to reduce respiratory tract infections and mortality in adults receiving intensive care. *Cochrane Database Systematic Review* 2009; 4:CD000022.
5. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F et al. Comparison of 8 vs 15 Days of Antibiotic Therapy for Ventilator-Associated Pneumonia in Adults: A Randomized Trial. *JAMA* 2003; **290**: 2588-98.
6. Zilberberg MD, Shorr AF. Ventilator-Associated Pneumonia: The Clinical Pulmonary Infection Score as a Surrogate for Diagnostics and Outcome. *Clin Infect Dis* 2010; **51(S1)**: S131-5.