18.4.3 Nosocomial pneumonia 4022 Wei Shen Lim

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section 18 Respiratory disorders 4022 FURTHER READING Briel M, et al. (2018). Corticosteroids in patients hospitalized with community-acquired pneumonia: Systematic review and indi- vidual patient data meta analysis. Clin Infect Dis, 66(3), 346–54. doi: 10.1093/cid/cix801. Kolditz M, Ewig S, Hoffken G (2013). Management-based risk predic- tion in community-acquired pneumonia by scores and biomarkers. Eur Respir J, 41, 974–84. Lee JS, Giesler DL, Gellad WF, Fine MJ. (2016). Antibiotic therapy for adults hospitalized with community-acquired pneumonia: A systematic review. JAMA, 315(6), 593–602. doi: 10.1001/ jama.2016.0115. Lim WS, et al. (2009). BTS guidelines for the management of commu- nity-acquired pneumonia in adults: update 2009. Thorax, 64 Suppl, iii1–55. Mandell LA, et al. (2007). Infectious Diseases Society of America/ American Thoracic Society consensus guidelines on the manage- ment of community-acquired pneumonia in adults. Clin Infect Dis, 44 Suppl 2, S27–72. National Institute for Health and Care Excellence (2014). Pneumonia in adults: diagnosis and management (CG191). https://www.nice.org. uk/guidance/cg191 Tomczyk S, et al. (2014). Use of 13-valent pneumococcal conju- gate vaccine and 23-valent pneumococcal polysaccharide vaccine among adults aged >/=65 years: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep, 63, 822–5. Welte T, Torres A, Nathwani D (2012). Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax, 67, 71–9. Wunderink RG, Waterer G (2017). Advances in the causes and manage- ment of community acquired pneumonia in adults. BMJ, 358, j2471. doi: 10.1136/bmj.j2471. 18.4.3 Nosocomial pneumonia Wei Shen Lim ESSENTIALS Nosocomial pneumonia is generally defined as a new pulmonary infiltrate on chest radiography, combined with evidence of infec- tion expressed as

fever, purulent respiratory secretions, and/or leucocytosis, with onset 48 hours or more after admission. It is the most frequent lethal nosocomial infection (overall mortality 7% in general ward inpatients to over 50% in critically ill patients). Aetiology—most cases are caused by Gram-negative bacteria
(50–70%) or Staphylococcus aureus (15–30%). Gram-negative bacteria reach the lung by aspiration of gastric contents or by microaspiration of upper airway secretions; throat cultures reveal that 60–75% of patients on intensive care units are colonized by these organisms (compared to 2–6% of healthy people). Prevention—simple methods of prevention are by nursing the pa- tient in the semi-upright position to reduce the risk of aspiration, and hand-washing between patients to prevent transmission of nosocomial pathogens. Diagnosis—this can be difficult, especially on intensive care units, when pulmonary infection is confirmed in only about 30% of cases of suspected ventilator-acquired pneumonia. Management—when empirical decisions are necessary in ser- iously ill patients, the favoured drugs directed against Gram-negative
bacteria are ceftazidime, cefepime, imipenem/meropenem, piperacillin/piperacillin–tazobactam, ticarcillin/ticarcillin–sulbactam, or ciprofloxacin. For methicillin-resistant S. aureus, vancomycin or linezolid is added. Introduction Definition Hospital-acquired pneumonia Hospital-acquired pneumonia (HAP) is defined as an inflam- matory condition of the lung parenchyma caused by infectious agents not present or incubating at the time of hospital admis- sion (i.e. pneumonia that occurs 48 hours or more after hospital admission). Hospital-acquired pneumonia is further classified into pneu- monias that occur on the intensive care unit (ICU HAP) and those that occur on the ward (non-ICU HAP) (Fig. 18.4.3.1). Ventilator- acquired pneumonia (VAP) is a subset of HAP that includes all pa- tients receiving mechanical ventilation at the time of infection. It is defined as HAP that develops more than 48 hours after endotracheal intubation. Aetiology Although most HAP occurs outside the ICU, knowledge about the microbiology of HAP is dominated by studies conducted HAP in the intensive care unit (ICU) (c.35%) Non-ICU HAP (c.65%) Ventilator-acquired pneumonia (VAP) (c.85%) Non-VAP ICU HAP (c.15%) Hospital-acquired pneumonia (HAP) Subdivisions of hospital-acquired pneumonia Fig. 18.4.3.1 Subdivisions of hospital-acquired pneumonia. HAP = hospital-acquired pneumonia. ICU = intensive care unit. VAP = ventilator-acquired pneumonia.

18.4.3 Nosocomial pneumonia 4023 in ICU settings. The pathogens associated with HAP vary according to ward environment (e.g. ICU vs. non-ICU, surgical vs. medical), patient factors (e.g. reason for being in hospital, im- mune status), and treatments received (e.g. type of surgery, prior antibiotics). There are considerable local and regional differences in the spectrum of pathogens encountered in HAP, including their in- cidence and antibiotic resistance profile. The spectrum of likely pathogens (Table 18.4.3.1) can be broadly classified according to the absence, or presence, of risk factors for multi-drug resistant (MDR) pathogens. These risk factors include: • Previous antimicrobial therapy • Hospital stay more than 4 days • Invasive ventilation more than 4 days • Malnutrition • Structural lung disease • Known upper airway colonization by MDR pathogens In patients who are immunosuppressed, other less commonly en- countered pathogens may also cause HAP, including Legionella sp., Pneumocystis jiroveci, Nocardia sp., Aspergillus sp., Candida sp., and cytomegalovirus. Epidemiology Hospital-acquired pneumonia HAP is the second commonest nosocomial infection, after urinary tract infections, with a crude overall rate of about 6 per 1000 dis- charges. The incidence rates of HAP vary depending on the hospital environment and patient groups affected. Most infections occur on non-ICU wards where reported rates range from 1.6 to 18 per 1000 hospital admissions. Only about 35% of HAP occurs in ICU settings, although the

incidence of HAP is greater among patients in the ICU compared to patients on general wards. HAP carries the highest mortality rate of all nosocomial infec- tions, varying from about 7% in patients on general wards to over 60% in patients on bone marrow transplant units. Ventilator-acquired pneumonia The overall rate of VAP is about 16 per 1000 ventilator days. The rate of contracting VAP has been described as 3% per day during the first week of mechanical ventilation (MV), 2% per day during week 2, and 1% per day thereafter. Rates of VAP are highest in trauma ICUs (Table 18.4.3.2). Between 10% and 20% of patients receiving more than 48 hours of mechanical ventilation will develop VAP. The mean duration of occurrence of VAP is around 5–7 days, with associated mortality ranging from 25% to 75%. Critically ill patients who develop VAP, compared with patients without VAP are twice as likely to die, have significantly longer ICU lengths of stay (mean = 6 days), and incur more than US$10 000 in additional hospital costs. However, it is less clear whether more patients die with VAP or because of VAP. The at- tributable mortality of VAP is estimated at about 13%, with higher mortality rates in surgical patients and patients with mid-range illness severity scores (such as the acute physiology and chronic health evalu- ation (APACHE) score). Attributable mortality is lowest (close to 0%) in trauma and medical patients, and in patients with low or high illness severity scores. Pathogenesis In general terms, pneumonia develops when pathogenic organisms gain entry to the lower respiratory tract, overwhelm lung defences, and cause inflammation in the lung parenchyma. Infections causing HAP can be considered to arise from endogenous or exogenous sources. Endogenous infection is the commonest. In health, the oropharynx of individuals is colonized by Gram- positive organisms mainly of streptococcal species and secretions from the larynx or pharynx are cleared by mucociliary action or the cough reflex. In patients who are unwell, the usual oropharyngeal colonizers are gradually replaced by Gram-negative enteric bacteria, Pseudomonas aeruginosa, and Staphylococcus sp. With increasing severity of illness, colonization by Gram-negative enteric bacteria increases, from about 6% of normal persons to nearly 75% of critic- ally ill patients Microaspiration of oropharyngeal secretions is the predom- inant mechanism by which organisms enter the lower airways. In patients who are mechanically ventilated, colonizing organisms together with oropharyngeal secretions form biofilms along the endotracheal tube cuff or within the tube lumen. From there, or- ganisms may be introduced into the lower airways. Pneumonia
Table 18.4.3.1 Pathogens most commonly associated with HAP In patients without risk factors for MDR pathogens In patients with risk factors for MDR pathogens: additional pathogens to consider Enterobacteriaceae • Escherichia coli • Klebsiella sp. • Enterobacter sp. Haemophilus influenzae Staphylococcus aureus Streptococcus pneumoniae Methicillin-resistance Staphylococcus aureus Extended-spectrum β-lactamase forming Enterobacteriaceae Pseudomonas aeruginosa Acinetobacter baumannii Stenotrophomonas maltophilia MDR, multi-drug resistant Table 18.4.3.2 Rates of VAP in different types of ICU—pooled results from global surveillance study Type of ICU Pooled mean VAP rate
(per 1000 ventilator days) 95% CI Trauma 40.0 37 to 44 Neurologic 28.1 23 to 34 Respiratory 27.7 25 to 30 Neurosurgical 20.9 19 to 23 Medical/surgical 18.4 18 to 19 Surgical 16.3 16 to 17 Medical cardiac 10.8 10 to 12 Medical 7.7 7 to 8 Overall 15.8 15 to 16

 ensues if these organisms are not then cleared by cellular defence mechanisms. Exogenous infection with nosocomial pathogens acquired from the hospital environment is much less common. Pathogenic organisms found on healthcare workers or medical devices can colonize the upper airways of vulnerable patients or be inhaled into the lower airways. Potential sources of exogenous infec- tion include ventilator circuits, humidifiers, bronchoscopes,

and nebulizers. Haematogenous spread of infection from distant sites to the re- spiratory tract occasionally occurs. Intravenous cannulas or urinary catheters are potential sources of such infections. Risk factors Risk factors for the development of HAP are those that: a) increase oropharyngeal or gastric colonization by pathogenic organisms; b) facilitate the entry of organisms into the lower airways; c) impair host lung defences. They can be broadly divided into modifiable or nonmodifiable fac- tors (Table 18.4.3.3). Clinical features Patients with HAP are, by definition, already receiving care within a hospital setting for another medical condition. Symptoms related to HAP are therefore superimposed on any pre-existing symptoms. In this situation, recognizing the early symptoms of HAP can be very difficult, particularly in patients who are already severely ill, such as those receiving treatment in ICUs. The cardinal symptoms of HAP are: • fever c.80% • cough c.85% • breathlessness c.70% • sputum production c.50% • chest pain c.45% While it is possible for HAP to develop without any specific symp- toms, this is unusual. The clinical signs associated with HAP are similar to those for CAP (see Chapter 18.4.2). These include fever, tachycardia, raised respiratory rate, hypoxia, and hypotension. On examination of the chest, signs of consolidation may be pre- sent. The frequency with which these signs occur is not well studied and vary according to the patient cohort. However, as these signs are not specific for HAP, the main challenge is in differentiating HAP from other causes that might be responsible for, or contributing to, any abnormal findings identified. Differential diagnosis Making a diagnosis of HAP or VAP can be very difficult. Conditions that mimic HAP include pulmonary infarction, adult respiratory distress syndrome, pulmonary oedema (with another infection site), pulmonary haemorrhage, vasculitis, interstitial lung disease, malig- nancy, and drug toxicity. Clinical investigation Making a diagnosis The objective of investigations in HAP is to confirm or refute the diagnosis as soon as possible. A chest X-ray (CXR) is essential to establishing the diagnosis with a sensitivity of 50–80%. However, the specificity of CXR changes for HAP is poor, especially for critic- ally ill patients being managed on the ICU. Similarly, general blood investigations and serum biomarkers may be abnormal for many reasons other than HAP. In clinical practice, it is widely accepted that a diagnosis of HAP should be suspected in a patient with new-onset or progressive in- filtrates on CXR in combination with two or more of the following criteria: • white cell count more than 10 000 or less than 4000/ul • fever more than 38.3°C • purulent respiratory secretions In these circumstances, isolation of a relevant pathogenic or- ganism from blood or respiratory samples confirms the diagnosis of HAP, but in many instances microbiological confirmation is not attained and the diagnosis of HAP may only be upheld based on the combination of ongoing compatible clinical features, the lack of an alternative diagnosis, and response to antimicrobial therapy. In patients with suspected VAP, a clinical pulmonary infection score has been advocated to improve the specificity of clinical diag- nosis. This combines clinical, radiological, physiological, and micro- biological (culture of tracheal aspirate) data into a single figure. However, it remains an imprecise diagnostic tool and its value is de- bated. Overall, in patients with suspected VAP, a pulmonary infec- tion is confirmed in only about 30%. Microbiological investigations When HAP is suspected, samples from all potential sites of noso- comial infection should be obtained for culture, preferably before antibiotic therapy is started. This includes blood, urine, and respira- tory samples. Table 18.4.3.3 Risk factors associated with HAP and VAP Nonmodifiable risk factors Modifiable risk factors • Advanced age • Male gender • Chronic lung disease • Diabetes • Immunosuppression • Cranial trauma • Neurosurgery • Extensive burns • Coma • Shock • Renal dysfunction • ARDS • Multiorgan failure • Smoking • Malnutrition • Supine positioning • Gastric overdistension • Nasal tubes • Endotracheal intubation • Colonization of ventilation circuits • Patient movement in and out of ICU

for investigations or procedures • Duration of hospital stay

18.4.3 Nosocomial pneumonia 4025 A range of respiratory samples—sputum, tracheobronchial aspirate (TBA), bronchoalveolar lavage (BAL)—may be obtained depending on whether the patient is being managed in ICU and is being mechanically ventilated. A bronchoscopy with BAL provides good-quality targeted lower re- spiratory airway specimens, but there is no good evidence that use of a BAL specimen for the diagnosis of HAP, compared to a TBA obtained in a sterile manner, results in reduced mortality, reduced time in ICU and on mechanical ventilation, or higher rates of antibiotic change. The decision to perform bronchoscopy in patients with suspected HAP or VAP should take into account all indications for and against bronchos- copy, not just the potential microbiological diagnostic yield. Measurement of biomarkers such as IL-1β, IL-8, procalcitonin, and type 1 soluble triggering receptor expressed on myeloid cells (sTREM-1) in BAL specimens or serum, may improve the diagnosis of HAP in future. Treatment Some general principles of treatment are widely recognized:

1. Delay in commencing appropriate antimicrobial therapy is asso- ciated with poorer outcomes.
2. Empirical combination therapy is mainly indicated when treating patients who are severely ill or at increased risk of infec- tion by MDR pathogens.
3. There are no clinical trials demonstrating clear superiority of one antimicrobial regimen over another.
4. Overuse of antimicrobial therapy should be avoided. De-escalation of antimicrobial therapy should start as soon as possible, even within 2–3 days of initiation of empirical treatment.
5. The duration of therapy does not usually need to exceed 8 days. In clinical practice, the combined difficulty in establishing a defini- tive diagnosis of HAP together with the consequences of failing to treat HAP in a timely manner, mean that patients with suspected HAP are usually treated aggressively at the outset, followed by an equally determined de-escalation plan based on regular clinical and microbiological re-assessments. Many national guidelines offer recommendations for the empir- ical therapy of HAP (Table 18.4.3.4), but given the large spectrum of possible pathogens and the variation in local resistance patterns, local intelligence of the prevailing microbiology is critical to the choice of empirical antimicrobial therapy. De-escalation and duration of therapy Following the initiation of antimicrobial therapy in patients with sus- pected HAP, daily review of the diagnosis should enable antibiotics to be discontinued if features of HAP do not evolve and the patient remains stable, and/or an alternative diagnosis becomes apparent. In patient where a positive microbiological diagnosis is obtained, de-escalation of therapy from broad spectrum to targeted antibiotics is usually possible and desirable. For patients treated initially with appropriate antibiotics, seven to eight days of antimicrobial therapy is usually suffi- cient, although patients infected with certain pathogens, such as Pseudomonas aeruginosa or methicillin-resistant Staphylococcus aureus (MRSA), may require longer treatment courses of up to 14 or 21 days. Prevention In hospital, general infection control measures have an important role in reducing cross transmission of pathogens and hence the de- velopment of healthcare-acquired infections, including HAP. These include simple measures such as universal hand hygiene, and use of personal protective equipment. For patients awaiting elective surgery, smoking cessation and the maintenance of good nutrition during the preoperative period are important

preventive measures. Prevention of ventilator-acquired pneumonia Most of the evidence for preventive strategies relate to HAP occurr ing on the ICU and to VAP (Table 18.4.3.5). Nonpharmacological approaches to the prevention of VAP are generally aimed at reducing or preventing aspiration of oropharyngeal and gastric secretions. Duration of mechanical ventilation Strategies to reduce the duration of mechanical ventilation include the use of weaning protocols, limiting the use of sedation and avoiding reintubation. Noninvasive ventilation (NIV) may be used to both avoid mechanical ventilation in the first instance, or as a means of supporting early extubation. It has been shown to lower the risk of VAP and reduce mortality. Table 18.4.3.4 A guide to empirical antimicrobial therapy in HAP (based on various national guidelines) I. Patients not at risk of MDR pathogens β-lactamase stable β-lactam (e.g. coamoxiclav), or 3rd generation cephalosporin (e.g. cefotaxime), or Respiratory fluoroquinolone (e.g. levofloxacin) II. Patients at increased risk of MDR pathogens β-lactam active against Pseudomonas aeruginosa Piperacillin/tazobactam, or Anti-pseudomonal cephalosporin (e.g. cefepine or ceftazidime), or Carbapenem (e.g. meropenem) Plus Fluoroquinolone (e.g. ciprofloxacin), or Aminoglycoside (e.g. amikacin) Plus (if increased risk of MRSA) Vamcomycin, or linezolid Table 18.4.3.5 Prevention of VAP Nonpharmacological approaches Reduce the time of mechanical ventilation • Use of noninvasive ventilation (NIV) • Weaning protocols • Sedation protocols Avoid re-intubation Reduce endotracheal tube colonisation and microaspiration • Subglottic suctioning • Head of bed elevation above 30 degrees • Antimicrobial-coated endotracheal tube Pharmacological approaches Selective digestive tract decontamination (SDD) Selective oropharyngeal decontamination (SOD) Oral decontamination

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Revision #1
Created 2026-01-22 16:40:24 UTC by Omar Ayman
Updated 2026-01-22 16:40:24 UTC by Omar Ayman