Epidemiology, etiology, and risk factors of bacterial pneumonia

Epidemiology

Hospital-acquired pneumonia

Hospital-acquired pneumonia (HAP) is the second most common nosocomial infection after urinary tract infections. The incidence of HAP ranges from 5 to 15 cases per 1000 hospital admissions, and is a frequent problem in general wards (incidence ranging from 1.6 to 3.67 cases per 1000 admissions) [1–3]. In the case of patients admitted to an intensive care unit (ICU), HAP occurs in up to 25% of patients [4], with approximately 70 to 80% of episodes occurring during mechanical ventilation (MV) [5] (Figure 2.1).
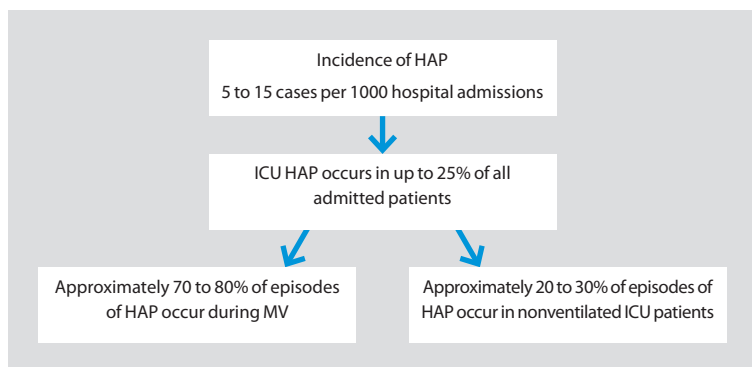

Figure 2.1 Distribution of hospital-acquired pneumonia [1–5]. HAP, hospital-acquired pneumonia; ICU, intensive care unit; MV, mechanical ventilation.

The incidence of HAP in the ICU varies by geographic area (Table 2.1). In the United States, the National Nosocomial Infection Surveillance data found that 31% of all nosocomial infections in combined medical–surgical ICUs were due to pneumonia, with 83% of cases being ventilator-associated pneumonia (VAP) [6]. In Europe, a large Italian study in 125 ICUs (which included 34,472 patients) reported that 9.1% of all admitted patients developed nosocomial infections, and pneumonia (specifically VAP) was the most prevalent (48.7%) ICU-acquired infection [7]. In a prevalence study of 254 ICUs in Mexico, 23.2% of patients had an ICU-acquired infection, and VAP was the most prevalent infection (41.2%) [8]. According to a study in Asian hospitals, the proportion of ICU-acquired respiratory infections ranges from 9 to 23% [9].

Most of the currently available studies on HAP have focused on ventilated patients; there are few studies on HAP in nonventilated ICU-acquired pneumonia (NV-ICUAP). One study that compared VAP and NV-ICUAP in a population of 315 patients with ICU-acquired pneumonia, found that 52% of patients had VAP and 48% had NV-ICUAP [5].

With all the data available relating to HAP in the ICU we can say that HAP represents one of the most common nosocomial infections worldwide and VAP is the most common nosocomial infection diagnosed in the ICU. The true incidence of NV-ICUAP remains uncertain.

Community-acquired pneumonia

Since community-acquired pneumonia (CAP) is not a reportable disease, its true incidence remains uncertain. Only 20 to 50% of patients with CAP require hospitalization. The overall annual incidence of CAP in adults in Europe ranges between 1.07 and 1.20 per 1000 person-years and 1.54 and 1.70 per 1000 population and increases with age (14 per 1000 person-years in adults aged ≥65 years) [22] (Table 2.2). CAP most frequently affects individuals at extremes of age and those with any type of coexisting illness [22–24]. The study by Torres et al [22] reported an increased risk of CAP in men (compared with women) and in patients ≥65 years of age.

Based on data from a systematic literature review, Said et al [28] estimated that the proportion of pneumococcal pneumonia that is

Study	Country/Year of publication	Study period	Population	Incidence
Torres et al [10]	Spain/1991	April 1987 to May 1988	VAP	78 (24%) per 322 cases
Rello et al [11]	Spain/1991	January 1988 to November 1989	VAP	58 (21.9%) per 264 cases
Joseph et al [12]	India/2009	October 2006 to December 2007	VAP	22.94 per 1000 ventilator days
Blot et al [13]	Belgium, France, Germany, Greece, Italy, Ireland, Portugal, Spain, and Turkey/2014	The period of data collection was 6 months	VAP	14.6% in patients 45 to 64 years of age; 17.0% in patients 65 to 74 years of age; 12.8% in patients ≥75 years of age
Suka et al [14]	Japan/2007	July 2002 and June 2004	VAP	53.4%; 6.5 cases per 1000 patient-days
Sopena et al [15]	Spain/2014	January 2006 and April 2008	Non-ICU HAP	2.45 cases per 1000 hospital admissions (95% CI, 2.04–2.92)
Barreiro-Lopez et al [16]	Spain/2005	November 1997 to January 1999	Non-ICU HAP	3.35 cases per 1000 hospital admissions
Franzetti et al [17]	Italy/2006	January 1988 and December 2002	NBP (HIV)	24 cases per 1000 inpatient/year
Weber et al [18]	USA/2007	2000 to 2003	HAP/VAP	0.37 cases per 1000 hospital admissions
Diouf et al [19]	France/2006	January to December 2002	VAP	7.16 per 100 admitted patients and 50 per 100 ventilated patients
Koulenti et al [20]	Belgium, France, Germany, Greece, Italy, Ireland, Portugal, Spain, and Turkey/2009		HAP/VAP	75.9% NP; 20.5% HAP; 42.7% VAP; 12.7% VE-VAP
Japoni et al [21]	Iran/2011	June 2008 and March 2009	HAP/VAP	6.9% NP, of which 72% were VAP

Table 2.1 Incidence of hospital-acquired pneumonia. HAP, hospital-acquired pneumonia; HIV, human immunodeficiency virus; ICU, intensive care unit; NBP, nosocomial bacterial pneumonia; NP, nosocomial pneumonia; VAP, ventilator-associated pneumonia; VE-VAP, very early-onset ventilator-associated pneumonia. Data extracted from [10–21].

Study	Country	Study period	CAP incidence (95% CI)
Rodriguez et al [25]	UK	1 January 2000 to 31 December 2005	Primary care patients, per 1000 person-years: • Overall, 1.07 (1.04 to 1.09) • Women, 0.93 (0.89 to 0.96) • Men, 1.22 (1.18 to 1.26)
Vila-Corcoles et al [26]	Spain	1 January 2002 to 30 April 2005	Age ≥65 years, per 1000 person-years: • Overall, 14.0 (12.7 to 15.3) • Men, 19.2 (17.1 to 21.6) • Women, 10.0 (8.6 to 11.5)
Viegi et al [27]	Italy	15 February 1999 to 14 February 2000	Annual incidence per 1000 population: • Overall, 1.703 • Males, 1.692 • Females, 1.713

Table 2.2 Epidemiology of community-acquired pneumonia in Europe. Data extracted from Rodriguez et al [25], Vila-Corcoles et al [26], and Viegi et al [27].

bacteremic to be approximately 25%, and the ratio of nonbacteremic pneumococcal pneumonia to bacteremic pneumococcal pneumonia to be approximately 3:1.

Estimates of mortality among patients with CAP range from 1 to 5% in outpatients, from 5.7 to 14.0% in general wards, and from 34 to 50% in the ICU setting (especially in ventilated patients) [29,30]. Medium- and long-term mortality of patients with CAP who were enrolled in the Pneumonia Patient Outcomes Research Team (PORT) cohort study was 8.7% within 90 days after presentation, 29.2% in 1 year, and 25.4% in 5 years [31].

In the case of pneumococcal pneumonia, the mortality rate is about 5%, and in the case of bacteremic pneumococcal pneumonia the mortality rates vary significantly, ranging from 6 to 30% in the adult population [32,33].

Microbial etiology

Etiology of hospital-acquired pneumonia

Knowledge of pathogens associated with HAP is critical for empirical antibiotic therapy. Most data concerning the microbial etiology of HAP refer specifically to the VAP population; data on microbial etiology of NV-ICUAP and non-ICU HAP remain limited.

The principal sources of pathogens in HAP cases are the health care environment and the patient's own microbial flora. The microbial etiology of HAP in the ICU varies according to patient population, hospital ICU settings, the country, and the type of presentation (early- or late-onset).

A review of published studies of the causes of pneumonia in hospitalized patients and the results of the SENTRY Antimicrobial Surveillance Program in the United States [34] concluded that six pathogens cause approximately 80% of HAP cases (Figure 2.2): *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella* species, *Escherichia coli*, *Acinetobacter* species, and *Enterobacter* species.
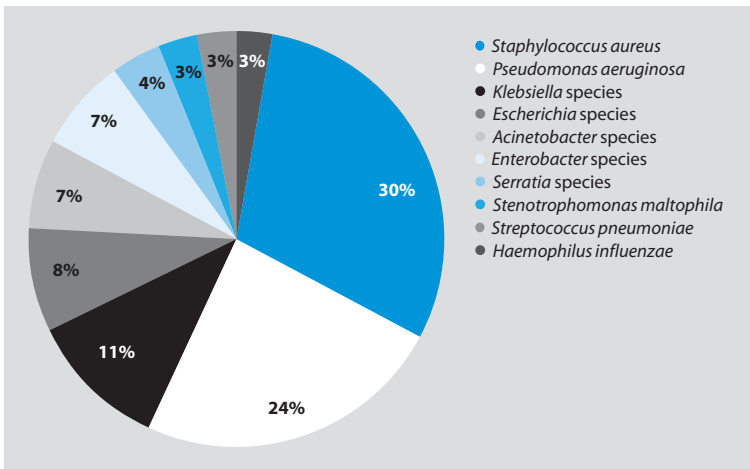

Figure 2.2 Microbial etiology of hospital-acquired pneumonia (SENTRY study). Data extracted from Jones [35].

Gram-negative pathogens

The most frequent Gram-negative pathogens associated with HAP include:

- *P. aeruginosa*;
- *Acinetobacter baumannii*;
- *Haemophilus influenzae;* and
- *Enterobacteriaceae* (*Klebsiella pneumoniae, E. coli, Enterobacter* species, *Serratia* species*, Proteus* species, etc).

Gram-negative bacteria are implicated in 50 to 80% of the cases of HAP in an ICU [10].

Gram-positive pathogens

The most common Gram-positive pathogens isolated from patients with HAP include *S. aureus* (methicillin-sensitive and methicillin-resistant), *Streptococcus* species*,* and *Streptococcus pneumoniae.* Gram-positive pathogens account for 20 to 30% of HAP cases.

Polymicrobial etiology

Polymicrobial etiology is defined as pneumonia caused by more than one potentially pathogenic microorganism, and around 30 to 70% of VAP cases are polymicrobial [36,37]. Combes et al [37] demonstrated that the epidemiology and outcomes of patients with pneumonia of monomicrobial or polymicrobial etiology did not differ significantly.

Etiology of early- and late-onset pneumonia

Early-onset HAP in patients with no prior antibiotic exposure is often caused by community-acquired pathogens such as *H. influenzae, S. pneumoniae,* or methicillin-sensitive *S. aureus* (MSSA), and in these cases pathogens with antibiotic resistance are rarely causative. Patients with prior antibiotic exposure are susceptible to the above microorganisms plus some *Enterobacteriaceae* (*Serratia* species and *Proteus* species).

Patients with late-onset HAP have the most severe form of infection and are at an increased risk of infection by multidrug-resistant (MDR) microorganisms such as *P. aeruginosa*, methicillin-resistant *S. aureus* (MRSA), *A. baumannii*, and *Enterobacteriaceae* expressing extended
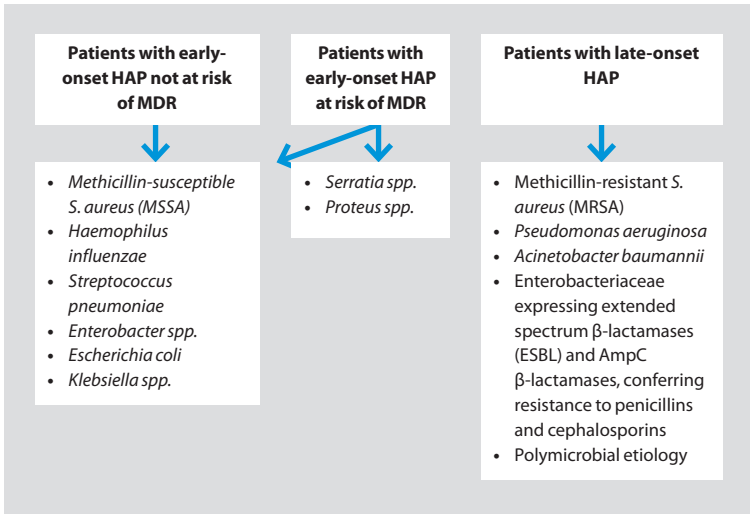
Patients with early-onset HAP not at risk of MDR	Patients with early-onset HAP at risk of MDR	Patients with late-onset HAP
• *Methicillin-susceptible S. aureus (MSSA)* • *Haemophilus influenzae* • *Streptococcus pneumoniae* • *Enterobacter spp.* • *Escherichia coli* • *Klebsiella spp.*	• *Serratia spp.* • *Proteus spp.*	• Methicillin-resistant *S. aureus* (MRSA) • *Pseudomonas aeruginosa* • *Acinetobacter baumannii* • Enterobacteriaceae expressing extended spectrum β-lactamases (ESBL) and AmpC β-lactamases, conferring resistance to penicillins and cephalosporins • Polymicrobial etiology

Figure 2.3 Microbial etiology of early- and late-onset pneumonia. HAP, hospital-associated pneumonia; MDR, multidrug-resistant.

spectrum β-lactamases (ESBL) and AmpC β-lactamases, which confer resistance to penicillins and cephalosporins. Polymicrobial etiology may also be seen in patients with late-onset HAP. Prior antibiotic therapy or prior hospitalization within 90 days of infection predisposes to colonization and infection with MDR pathogens [38] (Figure 2.3).

Multidrug-resistant pathogens

Pathogens such as *P. aeruginosa, S. aureus* (MRSA), *A. baumannii*, and ESBL-producing enteric Gram-negative bacilli continue to increase in frequency and in resistance profiles in ICUs around the world.

Goossens [39] in the MYSTIC study reported that 12% of isolates from 33 European ICUs were *P. aeruginosa* MDR (resistant to ceftazidime, ciprofloxacin, and gentamicin). The prevalence of *P. aeruginosa* is due to its ability to acquire antibiotic resistance, especially in cases of previous colonization, previous infection with MDR *P. aeruginosa,* and prior antibiotic therapy during an ICU stay. VAP caused by *P. aeruginosa* is associated with a high mortality [40].

HAP caused by *A. baumannii* represents approximately 20% of all episodes of HAP in ICUs in Europe [20]. The success of *A. baumannii* is due to its high environmental resistance, limited virulence, and an extraordinary facility for the development of antimicrobial resistance.

Etiology of community-acquired pneumonia

The differing percentages of causative microorganisms associated with CAP that have been reported in studies are likely to be due to a number of factors, including diversity in local epidemiology, setting (outpatients, hospitalized, or ICU), pneumonia severity, and patient characteristics (eg, sex, age, and comorbidities). However, *S. pneumoniae* is widely accepted as being the most common CAP-causing pathogen across a range of severities and patient ages [41–44]. In Europe and the United States, *S. pneumoniae* accounts for about 30 to 35% of cases [41,45,46].

The frequencies of atypical bacteria varies according to the epidemic year, but are still considered common causes of CAP [44]. Among these, *Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Legionella pneumophila* are the most frequently reported. *M. pneumoniae* accounts for up to 37% of CAP in patients treated as outpatients and 10% of cases requiring hospitalization [41,47]. *C. pneumoniae* accounts for 5 to 15% of

Outpatients	Hospitalized (Non-ICU)	ICU patients
Streptococcus pneumoniae	*Streptococcus pneumoniae*	*Streptococcus pneumoniae*
Mycoplasma pneumoniae	*Mycoplasma pneumoniae*	*Legionella pneumophila*
Haemophilus influenzae	*Chlamydia pneumoniae*	Gram-negative bacilli
Chlamydia pneumoniae	*Haemophilus influenzae*	*Staphylococcus aureus*
Respiratory viruses: influenza A and B, adenovirus, RSV, parainfluenza virus	*Legionella pneumophila*	Respiratory viruses
	Respiratory viruses	*Haemophilus influenzae*
	Polymicrobial etiology	*Pseudomonas aeruginosa* (the frequency is determined by the presence or absence of specific risk factors)
		Polymicrobial etiology

Table 2.3 Microbial etiology of community-acquired pneumonia by site of care. Adapted from Cillóniz et al [41]. ICU, intensive care unit; RSV, respiratory syncytial virus.

cases of CAP [41], and *L. pneumophila* pneumonia accounts for 2 to 6% of CAP in immunocompetent patients (especially serogroup 1) [48].

In the case of respiratory viruses, data show a viral presence in 10 to 30% of immunocompetent adults hospitalized with CAP [41,49,50]. Influenza virus A/B, respiratory syncytial virus, adenovirus, rhinovirus, and parainfluenza virus are most often responsible for CAP in inmuno-competent adults.

The incidence of polymicrobial etiology in CAP varies from 5.7 to 13.0% depending on the population and the microbiological diagnostic test used [41,50,51]. Table 2.3 shows the principal pathogens involved in CAP.

Antibiotic resistance

Antibiotic resistance among *S. pneumoniae,* the most common cause of CAP, has increased worldwide in the last two decades [52–54]. However, mortality rates related to antibiotic-resistant *S. pneumoniae* have not increased due to interventions such as conjugated pneumococcal vaccine, which covers the serotypes that are most likely to express resistance [55]. In a study of macrolide-resistant *S. pneumoniae,* Daneman et al [56] found that resistance, and therefore risk of macrolide failure, was independent of the underlying resistance mechanism.

Pneumococcal strains have developed resistance to several anti-biotics including penicillins, cephalosporins (β-lactams), macrolides, and fluoroquinolones. Currently, 20 to 30% of pneumococcal disease cases worldwide are MDR (resistant to more than three classes of antibiotics) [57,58] (Table 2.4).

It is broadly recognized that risk factors for infection caused by antimi-crobial-resistant *S. pneumoniae* include extremes of age (age <2 years or >65 years), antimicrobial treatment within the previous 3 months, com-munity or household exposure to resistant isolates, institutionalization, alcoholism, comorbidity, and immunosuppression [60,61]. A prospective cohort study of invasive pneumococcal infection conducted in Canada aimed to investigate the relative risk of infection with macrolide- or fluoroquinolone-resistant *S. pneumoniae* on the basis of antibiotic use in the previous 3 months [62]. The prevalence of macrolide resistance among infecting isolates increased from 7% to 10% (when no antibiotic,

Pathogens	Antibiotic resistance	Principal mechanisms of resistance	Risk factors of resistance
Community-acquired pneumonia			
Streptococcus pneumoniae	Penicillins	Mutations in PBPs 2x, 2b, and 1a	Prior antibiotic treatment
		Methylation of the 23S ribosomal target site, encoded by the *erm(B)* gene	Age <5 years
			Attendance to day-care centers
	Macrolides	Active (proton-dependent) efflux, encoded by the *mefE* (macrolide efflux) or *mefA* genes	Residence in long-term care facilities
			Recent hospitalization
			Chronic pulmonary disease
			Nosocomial acquisition
	Fluoroquinolones	Mutations in the QRDR of *gyrA* and/or *parC*	Older age
			Prior exposure to fluoroquinolones
Mycoplasma pneumoniae	Macrolides	Mutation in the 23S gene rRNA	
Hospital-acquired pneumonia			
Staphylococcus aureus	Methicillin (MRSA)	Gene *mecA*	Hospital environment (ICU)
	Vancomycin (VRSA)	Presence of transposon Tn1546	Prolonged hospitalization (>5 days)
	Daptomycin	*mprF* and the *yycFG* components of the *yycFGHI* operon	Recent hospitalization for 2 days in the preceding 90 days
Pseudomonas aeruginosa	Penicillins	Reduced access to bacterial targets	
	Aminoglycosides	Presence of efflux mechanisms	Recent antibiotic therapy
	Fluoroquinolones	Production of enzymes that inactivate and degrade antibiotics	Residence in a nursing home or extended care facility
Acinetobacter baumannii	Penicillins	Antimicrobial-inactivating enzymes	Immunosuppressive therapy or disease
	Carbapenems	Reduced access to bacterial targets	
	Colistin		
	Tigecycline	Mutations that change targets or cellular functions	
	Fluoroquinolones		

Table 2.4 Antibiotic resistance and risk factors associated with common pathogens causing pneumonia. Adapted from Lynch and Zhanel [52] and Feldman et al [59]. *Erm(B),* erythromycin ribosome methylation; *mprF*, multipeptide resistance factor; PBPs, penicillin-binding proteins; QRDR, quinolone resistance determinant region.

an antibiotic from another class, or erythromycin had previously been used) to 53% if azithromycin had previously been used. Similarly, the prevalence of fluoroquinolone resistance among pneumococci recovered from adults with community-acquired infection was <1% if no fluoroquinolone had been used in the previous 3 months, rising to approximately 4% if a fluoroquinolone had previously been used [62].

S. pneumoniae was reported to be the etiological agent in 2 to 35% of cases of CAP treated in the outpatient setting [42,63,64]. It is estimated that 0.14 to 1.90% of outpatients with bacterial pneumonia have pneumococcal infections with levels of resistance high enough to warrant consideration of alternative treatment [65].

Approximately 10% of CAP cases are caused by MDR pathogens (*S. aureus* and *P. aeruginosa* were most frequently isolated) [66,67]. In a European study of pathogens isolated from hospitalized patients with CAP, MDR pathogens were the cause of CAP in 3.3 to 7.6% of patients in which a pathogen could be identified, with MRSA being the most common MDR pathogen [68].

Hospital environments, especially ICUs, are important reservoirs of resistant pathogens. The risk of developing infection with MDR pathogens in HAP depends on the presence of some risk factors such as prolonged hospitalization (>5 days), recent hospitalization for 2 days in the preceding 90 days, recent antibiotic therapy, residence in a nursing home or extended care facility, immunosuppressive therapy, or comorbidity.

MDR pathogens are mostly involved in late-onset HAP due mainly to antibiotic selective pressure, cross-transmission, and colonization from ICU environmental sources. *S. aureus* (especially MRSA) accounts for up to 30% of cases of HAP [69], compared to less than 10% of CAP cases [48].

Colonization (nasal and skin) is the major source for pneumonia; 30 to 50% of healthy adults carry pneumonia-causing pathogens transiently in the anterior nares, and health care workers may have higher carriage rates. Patients who develop MRSA pneumonia have nasal colonization on admission in 67% of cases, whereas noncolonized patients have less than a 5% risk of subsequent MRSA pneumonia. This pathogen is easily transferred from person to person by direct hand contact.

Community-acquired MRSA (CA-MRSA) has become an important CAP pathogen. Community and hospital MRSA share a *mecA* gene that confers universal methicillin- and β-lactam-resistance, but CA-MRSA presents broader antibiotic susceptibility than hospital MRSA. CA-MRSA carries the gene for the Panton-Valentine leukocidin (PVL) toxin, which causes leukocyte destruction and tissue necrosis [70]. The clinical presentation of CA-MRSA pneumonia has been described as the presence of a cavitary lung lesion. CA-MRSA is susceptible to clindamycin, TMP-SMX, daptomycin, and doxycycline [71].

P. aeruginosa in CAP is rare; patients with underlying diseases such as cystic fibrosis, chronic obstructive pulmonary disease (COPD), and bronchiectasis are the most likely to be affected by this pathogen. *P. aeruginosa* is a leading cause of HAP and particularly frequent cause of VAP [72]. Prolonged endotracheal intubation and prior antibiotic therapy, especially with broad-spectrum antibiotics, are the primary risk factors for *Pseudomonas* VAP. A French study of patients with VAP noted that patients with prior antimicrobial therapy had markedly increased rates of *P. aeruginosa* or *Acinetobacter* infection (65%) compared with patients with VAP without prior antibiotic therapy (19%) [73].

A. baumannii exhibits a high level of antimicrobial resistance but with a low virulence [74] and can cause CAP and HAP. *A. baumannii* is a frequent cause of pneumonia in Southeast Asia; hot climates especially dry [75] and humid [76,77] are the preferred environment of this pathogen. Infections caused by *A. baumannii* presented similar epidemiologic patterns in CAP and HAP, with a seasonal variation and a peak in the late summer. CAP caused by *A. baumannii* has a mortality rate of 50% [76], and in the case of HAP the severity of the underlying disease determines the fatality rate. Garnacho-Montero et al [74] noted that antibiotic exposure was the only independent risk factor associated with VAP caused by *A. baumannii*. The mortality rate of VAP caused by *A. baumannii* infection was no higher than VAP caused by other pathogens.

Patient-related factors	Hospital- and treatment-related factors
Male sex	Colonization of the oropharynx by virulent microorganisms
Age 60 years or above	
Malnutrition	Prior antibiotic therapy
Severe acute or chronic illnesses	Conditions that promote pulmonary aspiration or inhibit coughing
Immunosuppression	
Recent hospitalization	• thoracoabdominal surgery
Burns, trauma, post surgery	• endotracheal intubation
Severity of illness (APACHE II or SAPS II score)	• insertion of nasogastric tube
Acute respiratory distress syndrome (ARDS)	• inadequate endotracheal tube cuff pressure
	• repeated reintubation
	• supine position
	Exposure to contaminated respiratory equipment

Table 2.5 The factors that increase the risk of developing hospital-acquired pneumonia.
Adapted from Sopena and Sabria [1] and Masterton et al [78].

Risk factors

Risk factors related to hospital-acquired pneumonia

Factors that increase the risk of HAP include two main categories and are detailed in Table 2.5.

Intubation and mechanical ventilation increases the risk of VAP by 6- to 21-fold, and the risk is greatest in the first 5 days of intubation [38]. The endotracheal tube allows direct entry of bacteria into the lower respiratory tract, interferes with normal host defense mechanisms, and becomes a reservoir for pathogenic microorganisms.

Oropharyngeal colonization is the main mechanism responsible for development of HAP; colonization will be present upon admission or acquired in the ICU. Feldman et al [59] found that colonization and biofilm formation were present within 12 hours of patient intubation and present in almost all patients after 96 hours. In the same study it was also demonstrated that colonization in patients undergoing mechanical ventilation occurred first in the oropharynx and stomach, then lower respiratory tract, and finally in the endotracheal tube [59].

Risk factors related to community-acquired pneumonia

Age and sex

Pneumonia can occur at any age, but its incidence increases significantly with advanced age. Old age is therefore an important risk factor for pneumonia, which is a leading cause of illness and death in the elderly. A recent study that investigated the influence of age and comorbidity on microbial patterns in patients over 65 years of age with CAP found that age does not significantly affect pathogen patterns, whereas comorbidities were associated with specific causes [23]. The main factors associated with mortality in this analysis were neurologic diseases, the presence of potential MDR pathogens, and very advanced age (>85 years) [23]. Advanced age is associated with a decline in the integrity of physical barriers and protection against invading pathogens, as well as age-related changes in the immune system. Declines in the sensitivities of airway protective cough and swallowing reflexes are age-related and important risk factors for the development of pneumonia [79].

The difference of susceptibility to infections such as pneumonia between males and females is multifactorial. During the development of infection there is an interaction between sex-specific immune responses and immune responses to specific pathogens. A clear example of this relationship is the sex differences in the incidence and outcome of influenza virus A infections. In 2010 the WHO published a report detailing evidence that sex and gender should be considered when evaluating exposure to and the outcome of influenza virus infection [80]. The report concluded that the outcome of pandemic influenza H1N1 is generally worse for young adult females.

Health care settings

The number of patients who receive care outside the hospital setting (eg, in nursing homes) is increasing with the aging population, implying an increase in the risk of pneumonia [22,81,82]. In addition, 10 to 18% of all patients hospitalized for pneumonia are nursing home residents, with mortality rates potentially as high as 55% [81,83].

Comorbidities and lifestyle factors

Chronic obstructive pulmonary disease

COPD is one of the most common comorbidities associated with CAP. Patients with COPD have a 2- to 4-fold increased risk of CAP [22]. Data from a Spanish study conducted in patients with CAP compared the outcome of patients with and without COPD and revealed that the presence of COPD was an independent risk factor for mortality [84].

Diabetes mellitus and obesity

The prevalence of diabetes is increasing rapidly and is predicted to increase further, in parallel with the trends observed for obesity [85,86]. Diabetic patients may have increased susceptibility to pneumonia for several reasons: increased risk of aspiration, hyperglycemia, decreased immunity and impaired lung function, and coexisting morbidity.

Kornum et al [87] reported that Type 1 and Type 2 diabetes were risk factors for pneumonia-related hospitalization in a cohort of 34,239 patients with pneumonia in Denmark [87]. Similarly, Yende et al [88] reported that pre-existing diabetes was associated with a higher risk of death after hospitalization for CAP compared to those hospitalized for noninfectious illnesses. Furthermore, the risk of developing severe pneumococcal bacteremia is higher in diabetic patients [89].

Chronic renal disease

Several studies have demonstrated that chronic renal failure is a significant risk factor for mortality in patients with CAP [90,91]. In patients on dialysis, the mortality rate from pneumonia is 14- to 16-fold higher than in the general population [92].

Chronic liver disease

Bacterial infections occur in 32 to 34% of patients with cirrhosis who are admitted to the hospital, of which approximately 15% are pneumonia (the third leading cause of infection in these patients). Cillóniz et al [93] reported that chronic liver disease was a risk factor for pulmonary complication in patients hospitalized due to pneumococcal pneumonia [93].

Human immunodeficiency virus

CAP is a frequent respiratory complication in patients infected with human immunodeficiency virus (HIV), even in the highly active antiretroviral therapy era [94–96]. Patients infected with HIV are 25 times more likely to develop pneumonia than uninfected patients; the depletion of CD4+ lymphocytes and high levels of HIV-RNA in HIV-infected persons occurs in parallel to the risk of developing pulmonary infections [97].

Exposure to cigarette smoke

Smoking is associated with colonization by pathogenic bacteria and an increased risk of lung infections, especially in the case of pneumococcal pneumonia [98]. In a study of bacterial pneumonia in patients with HIV, current smokers had a >80% higher risk of developing pneumonia compared with never-smokers [33,99]. Bello et al [100] showed that current smokers with pneumococcal CAP often develop severe sepsis and require hospitalization at a younger age despite having fewer comorbid conditions. Almirall et al [101] found that passive smoking at home is a risk factor for CAP in older adults (65 years of age or more).

Alcohol abuse

Samokhvalov et al [102] performed a meta-analysis that showed that the consumption of 24, 60, and 120 g of pure alcohol daily resulted in a relative risk for incident CAP of 1.12 (95% CI 1.02–1.23), 1.33 (95% CI 1.06–1.67), and 1.76 (95% CI 1.13–2.77), respectively, relative to non-drinkers.

Poor oral hygiene

A hundred million bacteria (oral and respiratory bacteria) are contained in every cubic millimeter of dental plaque. Oral and respiratory bacteria in the dental plaque are shed into the saliva and are then aspirated into the lower respiratory tract and the lungs to cause infection. Aspiration pneumonia is one of the most serious problems in the elderly population.

Contact with children

Regular contact with children is associated with an increased risk of developing CAP [103]. Two studies have reported that the presence of

children in the household increased the adjusted odds ratio (OR) from 1.0 for 'no children' to 3.2 [104] or 3.41 [105] for three or more children.

Summary points

- CAP is a serious health problem associated with high morbidity and mortality in all age groups worldwide.
- HAP is the second most frequent nosocomial infection and is associated with significant impact on patient morbidity and mortality.
- *Streptococcus pneumoniae* remains the most common cause of CAP across all severities.
- Six pathogens cause approximately 80% of HAP: *S. aureus, P. aeruginosa, Klebsiella* species, *E. coli, Acinetobacter* species, and *Enterobacter* species.
- Pathogens involved in HAP differ significantly from those typically responsible for CAP.
- The etiological microorganisms associated with early-onset and late-onset HAP in patients with no prior antibiotic exposure are often the same as those responsible for CAP.
- MDR pathogens (*P. aeruginosa*, *A. baumannii*, and MRSA) are the most common pathogens in patients with late-onset HAP with prior antibiotic exposure.
- Older age, male sex, chronic comorbidities, exposure to cigarette smoke, alcohol abuse, malnutrition, conditions that promote pulmonary aspiration or inhibit coughing, and exposure to contaminated respiratory equipment are the principal risk factors for pneumonia.

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