Pneumonia

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Abstract | Pneumonia is a common acute respiratory infection that affects the alveoli and distal airways; it is a major health problem and associated with high morbidity and short-term and long-term mortality in all age groups worldwide. Pneumonia is broadly divided into community-acquired pneumonia or hospital-acquired pneumonia. A large variety of microorganisms can cause pneumonia, including bacteria, respiratory viruses and fungi, and there are great geographical variations in their prevalence. Pneumonia occurs more commonly in susceptible individuals, including children of <5 years of age and older adults with prior chronic conditions. Development of the disease largely depends on the host immune response, with pathogen characteristics having a less prominent role. Individuals with pneumonia often present with respiratory and systemic symptoms, and diagnosis is based on both clinical presentation and radiological findings. It is crucial to identify the causative pathogens, as delayed and inadequate antimicrobial therapy can lead to poor outcomes. New antibiotic and non-antibiotic therapies, in addition to rapid and accurate diagnostic tests that can detect pathogens and antibiotic resistance will improve the management of pneumonia.

Pneumonia is a common acute respiratory infection that affects the alveoli and distal bronchial tree of the lungs. The disease is broadly divided into community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP, which includes ventilation-associated pneumonia (VAP)) (BOX 1). Aspiration pneumonia represents 5–15% of all cases of CAP; however, its prevalence amongst patients with HAP is not known[1]. The lack of robust diagnostic criteria for aspiration pneumonia may explain why the true burden of this type of pneumonia remains unknown[1].

The causative microorganisms for CAP and HAP differ substantially. The most common causal microorganisms in CAP are *Streptococcus pneumoniae*, respiratory viruses, *Haemophilus influenzae* and other bacteria such as *Mycoplasma pneumoniae* and *Legionella pneumophila*. Conversely, the most frequent microorganisms in HAP are *Staphylococcus aureus* (including both methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA)), Enterobacterales, non-fermenting gram-negative bacilli (for example, *Pseudomonas aeruginosa*), and *Acinetobacter* spp.[2,3]. In health-care-associated pneumonia (HCAP), owing to patient risk factors, the microbial aetiology is more similar to that in HAP than to that in CAP. However, difficulties in standardizing risk factors for this population, coupled with the heterogeneity of post-hospital health care worldwide, suggest that the concept of HCAP has little usefulness, and indeed, HCAP was not included in recent guidelines for CAP and HAP[3–5].

Differences in microbiology between CAP and HAP depend on whether pneumonia was acquired in the community or health care environment and on host risk factors, including abnormal gastric and oropharyngeal colonization. In addition, the aetiopathogenesis of CAP is different from that of HAP. In general, mild CAP is treated on an outpatient basis, moderately severe CAP in hospital wards, and severe CAP in intensive care units (ICUs) with or without mechanical ventilation[6]. The need for mechanical ventilation is used as a sub-classification of interest for prognosis and stratification in randomized clinical trials.

Both CAP[7] and HAP[4] can occur in either immunosuppressed or immunocompetent patients. To date, most research data have been based on studies of immunocompetent patients and, therefore, we rely on such sources in this Primer. However, CAP, HAP and VAP in immunosuppressed patients have attracted the attention of researchers, and more investigation is to come.

In this Primer, we cover and summarize the most important and recent updates related to epidemiology, pathophysiology, diagnostic screening, prevention, management, quality of life, and research perspectives. Additionally, owing to the profound impact of the coronavirus disease 2019 (COVID-19) pandemic caused by

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severe acute respiratory syndrome (SARS) coronavirus 2 (SARS-CoV-2), we summarize the main features of SARS-CoV-2 pneumonia (BOX 2).

Epidemiology

Global incidence

Data from the 2019 Global Burden of Diseases (GBD) study[8] showed that lower respiratory tract infections (LRTIs) including pneumonia and bronchiolitis affected 489 million people globally. Children of <5 years of age and adults of >70 years of age are the populations most affected by pneumonia, according to the 2019 GBD study[8]. In 2019, there were 489 million incident cases of LRTI, and 11 million prevalent cases of LRTI. In the 2016 GBD study, the global incidence of LRTI was 155.4 episodes per 1,000 adults of >70 years of age and 107.7 episodes per 1,000 children of <5 years of age[9]. Finally, aspiration pneumonia contributes 5–15% of all cases of CAP and is associated with worse outcomes, especially in older patients with multiple comorbidities[10,11]. There is a lack of data about the incidence of aspiration pneumonia in patients with HAP[1,12].

In the USA, the Etiology of Pneumonia in the Community (EPIC) study[13] found that the annual incidence of CAP was 2.4 cases per 1,000 adults, with the highest rates amongst adults of 65–79 years of age (6.3 cases per 1,000 individuals) and those of ≥80 years of age (16.4 cases per 1,000 people). In Europe, the annual incidence of CAP has been estimated at 1.07–1.2 cases per 1,000 people, increasing to 14 cases per 1,000 people amongst those of ≥65 years of age and with a preponderance in men[14]. Differences in epidemiology between the USA and Europe might be explained by the higher proportion of the adult population who received the pneumococcal vaccine in the USA (63.6% of adults of ≥65 years of age, compared with pneumococcal vaccination rates of 20% to 30% in most European countries[15,16]); in addition, in 2015 in the USA, ~69% of adults of ≥65 years of age had received an influenza vaccine within the previous 12 months. Another possible contributing factor is the decreased rate of smoking in the USA: between 2005 and 2016, the percentage of smokers who quit increased from 51% to 59%[17]. Finally, marked differences between US and European health systems can influence epidemiological data.

The South American Andes region had the highest incidence of adults of >70 years of age with LRTIs (406.5 episodes per 1,000 people), while South Asia had the greatest number of LRTI episodes amongst adults of >70 years of age. Incidence per global region was 171.1 per 1,000 people in Central Europe, eastern Europe and central Asia; 234.4 per 1,000 people in Latin America and the Caribbean; 130.8 per 1,000 people in Southeast Asia, eastern Asia and Oceania; 246.6 per 1,000 people in North Africa and the Middle East; and 229.3 per 1,000 people in sub-Saharan Africa[9].

According to the 2016 GBD study[9], Oceania had the highest incidence of LRTI in children (171.5 per 1,000 children of <15 years of age), while South Asia had the greatest number of LRTI episodes amongst children of <5 years of age. Incidence per global region was: 107.1 per 1,000 children in Central Europe, eastern Europe, and central Asia; 94.9 per 1,000 children in Latin America and the Caribbean; 120.4 per 1,000 children in Southeast Asia, eastern Asia and Oceania; 133.2 per 1,000 children in North Africa and the Middle East; and 100.6 per 1,000 children in sub-Saharan Africa.

The epidemiology of pneumonia is constantly changing, owing to the development of molecular diagnostic tests, novel antimicrobial therapies and implementation of preventive measures. Since the beginning of the 21st century, pneumonia has been the most common cause of pandemic infections that have effects on its own epidemiology. In the 2009 influenza pandemic, the influenza virus A H1N1 infected ~200 million people and caused almost 250,000 deaths, with infectivity higher in children than in adults[18]. By contrast, in the current SARS-CoV-2 pandemic, 106 million people had been infected and >2 million had died worldwide by 9 February 2021. However, unlike the influenza virus A H1N1, SARS-CoV-2 affects adults more often than children[19].

VAP. The annual incidence of HAP in adults ranges from 5 to 10 cases per 1,000 hospital admissions globally, whereas VAP affects 10–25% of all patients on

Box 1 | **Classifications of pneumonia**

Community-acquired pneumonia (CAP)
Pneumonia acquired outside the hospital in individuals who have not been hospitalized during the month prior to symptom onset.

Hospital-acquired pneumonia (HAP)
Pneumonia acquired after at least 2 days of hospitalization and when no suspicion of disease incubation before hospital admission is present.

Ventilator-associated pneumonia (VAP)
HAP occurring >48 h after endotracheal intubation.

Aspiration pneumonia
Pneumonia occurring as a result of inhalation of contents from the stomach or mouth into the lungs. It is best considered as part of the continuum between CAP and HAP, and not as a distinct entity.

Health-care-associated pneumonia (HCAP)
Pneumonia acquired in non-hospital care institutions.

Box 2 | **COVID-19 features**

Frequent symptoms

- Fever
- Cough
- Shortness of breath

Less-common symptoms

- Headache
- Hyposmia (decreased sense of smell) and hypogeusia (decreased sense of taste)
- Sore throat
- Rhinorrhoea (runny nose)
- Muscle pain
- Diarrhoea and vomiting

Main complications

- Acute respiratory distress syndrome (ARDS)
- Sepsis and septic shock
- Multiple organ failure
- Secondary infection

mechanical ventilation[3]. HAP is the second most frequent hospital infection after urinary tract infection, and VAP is the most common cause of nosocomial infection and death in the ICU[3,4]. The incidence of HAP is highest amongst immunocompromised, post-surgical and older patients[20]. In the USA, the incidence of VAP is estimated to range from 2 to 6 cases per 1,000 ventilator-days[21], and the incidence of non-ventilator-associated HAP is estimated to be 3.63 cases per 1,000 patient-days[22]. A 2018 systematic review and meta-analysis of studies of VAP in adults from 22 Asian countries found an overall incidence of 15.1 cases per 1,000 ventilator-days[23]. In 2015, data from the prospective French multicentre OUTCOMEREA database (1996–2012) indicated that the risk of VAP was ~1.5% per ventilator-day, decreasing to <0.5% per day after 14 days of mechanical ventilation[24].

Mortality

The 2019 GBD study[8] showed that LRTI was responsible for >2.49 million deaths, with mortality highest amongst patients of >70 years of age (1.23 million deaths). These data indicate that mortality due to LRTI is higher than mortality due to tuberculosis (1.18 million deaths) and HIV (864,000 deaths), making it the leading cause of infectious disease mortality worldwide. Indeed, data from a systematic review and meta-analysis on the global and regional burden of hospital admissions for pneumonia estimated that 1.1 million pneumonia-related hospital deaths occurred in 2015 amongst older adults[25].

In 2016, the highest LRTI mortality rates amongst children of <5 years of age were in the Central African Republic (460 deaths per 100,000 children), Chad (425 deaths per 100,000) and Somalia (417 deaths per 100,000)[9]. Interestingly, data from the 2017 GBD study[26] showed that mortality due to LRTI decreased by 36.4% between 2007 and 2017 for children of <5 years of age, whereas it increased by an estimated 33.6% in adults of ≥70 years of age. LRTI-related deaths amongst children have substantially reduced as a result of the implementation of vaccines (against *S. pneumoniae* and *H. influenzae*), antibiotic therapy, the continuous improvements in education, nutrition, water, sanitation and hygiene, and female empowerment. Nevertheless, in many areas the progress is slow; Nigeria, India, Pakistan, Ethiopia and the Democratic Republic of Congo are the five countries with the highest child mortality[27].

Conversely, the increased mortality in adults of >70 years of age might be associated with the increasing longevity of the frail older population, chronic diseases, comorbidities[28], multiple medication use and functional disability, especially in high-income countries. In low-income countries, the high mortality is associated with the effect of air pollution; smoke and alcohol consumption are the main risk factors for pneumonia in this age group.

Globally, amongst children and adults, mortality in those with CAP is related to the treatment setting: <1% in outpatient care, ~4–18% in hospital wards and up to 50% in the ICU[29–31]. However, in adults, age and comorbidities influence mortality. A study that investigated the effects of age and comorbidities on CAP mortality found a mortality of 5% in patients of <65 years of age, 8% amongst patients of 65–79 years and 14% amongst patients of ≥80 years of age[32], and these rates increased to 20%, 42% and 43%, respectively, in patients with more than one comorbidity. On the basis of studies on long-term mortality across 1–10 years[33–35], approximately one in three adults will die within one year of being hospitalized with CAP[36]. The estimated in-hospital mortality in patients with chronic obstructive pulmonary disorder (COPD) and CAP has been reported to be 6% during hospitalization and 12%, 24% and 33% within 30 days, 6 months and 1 year from discharge, respectively[37]. Interestingly, 30-day mortality amongst those with pneumococcal pneumonia remained fairly stable in a 20-year study[33], and this was further confirmed in a review on the burden of pneumococcal CAP in Europe[38].

Globally, HAP and VAP are considered the leading causes of death due to hospital-acquired infection[39–41]. The estimated global mortality due to HAP is 20–30%, whereas global mortality due to VAP is 20–50%[20,42]. Mortality due to VAP in the USA was ~13%[4]. By contrast, a prospective study in central Europe[43] indicated that 30-day mortality due to VAP was 30%. In a large French cohort of patients admitted to the ICU for >48 h, both non-ventilator-associated HAP and VAP were associated with an 82% and a 38% increase in the risk of 30-day mortality, respectively[44]. However, analysis of data from trials on antibiotic therapy for bacterial HAP and VAP to characterize all-cause mortality showed that mortality differed notably within and across studies; all-cause mortality at day 28 was 27.8% in bacterial HAP, 18% in bacterial VAP and 14.5% in non-ventilation-associated bacterial HAP[45].

In a systematic review and meta-analysis[10], aspiration pneumonia was significantly associated with increased in-hospital mortality (relative risk 3.62) and 30-day mortality (relative risk 3.57) in patients with CAP treated outside of the ICU. One of the largest studies in aspiration pneumonia demonstrated that mortality in patients

with aspiration pneumonia (29%) was more than twice that in patients with CAP (12%)[11].

Risk factors and differences in epidemiology

CAP. Children of <5 years of age[46] and older adults[13], particularly those of of ≥65 years of age and with comorbidities[14,47], have an increased risk of CAP (TABLE 1). In children, prematurity, malnutrition, household air pollution, ambient particulate matter or suboptimal breastfeeding are the main CAP-related risk factors[48]. In adults, respiratory disease (for example, COPD), diabetes mellitus, cardiovascular disease and chronic liver disease are the most frequent comorbidities that increase the risk of CAP[14]. Of note, men have a higher risk of CAP than women, which may be explained by differences in anatomy, and behavioural, socioeconomic and lifestyle factors[49].

A US study on the incidence, outcomes and disease burden in >18,000 hospitalized patients with COPD[37] found that, during the 2-year study, 3,419 patients had pneumonia; the annual incidence for CAP was 93.6 cases per 1,000 in the COPD population. In patients without COPD, the incidence was 5.09 cases per 1,000. In the USA, 506,953 adults with COPD are estimated to be hospitalized every year due to pneumonia[37].

Immunocompromised patients have a higher risk of CAP than the general population[7,14]. A secondary analysis of an international, multicentre study from 54 countries worldwide found that almost one in five patients hospitalized with CAP were not immunocompetent[7]. Amongst patients with CAP, 18% had one or more risk factors for immunodeficiency, with chronic steroid use (45%), haematological cancer (25%) and chemotherapy (22%) being the most frequent.

Several studies have also demonstrated an association between lifestyle factors and the risk of CAP, including smoking, high alcohol consumption, being underweight (owing to under-nutrition or underlying conditions that compromise the immune response), living conditions, such as a large household or regular contact with children, and others[14]. Smoking is associated with colonization by pathogenic bacteria and an increased risk of lung infection, especially by *S. pneumoniae*[50]. Consumption of 24 g, 60 g and 120 g of pure alcohol daily (one standard alcoholic beverage equals 10 ml or 8 g of pure alcohol, and it is the approximate amount of alcohol that the average adult can process in an hour) resulted in relative risks for CAP of 1.12, 1.33 and 1.76, respectively, compared with no consumption[51]. In addition, exposure to air pollution may increase the risk of pneumonia in the short and long term; a study in 345 hospitalized patients with CAP and 494 controls (patients who were admitted in the same period but for non-pneumonia reasons) demonstrated that long-term exposure (1–2 years) to high levels of air pollutants (particulate matter 2.5 µm and nitrogen dioxide) was associated with increased hospitalization in those of ≥65 years of age[52].

HAP. Factors that increase the risk of HAP can be categorized into patient-related and treatment-related groups (TABLE 1). Oropharyngeal colonization is the main mechanism underlying HAP. However, much attention has been shifted to oropharyngeal colonization in critically ill patients (present at ICU admission or occurring during ICU stay)[53]. A study from Japan investigating oral colonization in residents in long-term care facilities found that 38% of these individuals were colonized with antibiotic-resistant pathogens, mainly *Acinetobacter* spp., Enterobacterales and *Pseudomonas* spp. The presence of these pathogens represents a potential risk for pneumonia[54]. Indeed, current international guidelines have suggested that previous colonization by antibiotic-resistant pathogens be considered when identifying patients with an increased risk of HAP due to such pathogens[3,4].

Colonization and biofilm formation were present within 12 h of intubation and remained for >96 h in most patients[55]. Underpinning an important association between intubation and VAP pathogenesis, this study also showed that colonization in patients undergoing mechanical ventilation occurred in the oropharynx and stomach first, followed by the lower respiratory tract and, thereafter, the endotracheal tube[55]. Intubation and mechanical ventilation can increase the risk of developing VAP by 6–21-fold, with the highest risk within the first 5 days of intubation[53]. Endotracheal tubes enable the direct entry of bacteria into the lower respiratory tract, interfere with normal host defence mechanisms and serve as a reservoir for pathogenic microorganisms.

Multiple risk factors are related to aspiration pneumonia, each one increasing the chance of gastric contents reaching the lungs. The most frequent of these factors are impaired swallowing, decreased consciousness and an impaired cough reflex[1] (TABLE 1).

Table 1 | **Risk factors for CAP, HAP and aspiration pneumonia**

CAP	HAP	CAP and HAP	Aspiration pneumonia
Lifestyle factors (smoking, excessive alcohol consumption, poor oral hygiene and frequent contact with children); previous episode of pneumonia	Male sex; malnutrition; burns, trauma, and post surgery; severity of illness; acute respiratory distress syndrome (ARDS); colonization of the oropharynx by virulent microorganisms; previous antibiotic therapy; conditions that promote pulmonary aspiration or inhibit coughing (thoracoabdominal surgery, endotracheal intubation, insertion of nasogastric tube, inadequate endotracheal tube cuff pressure, repeated reintubation, supine position, exposure to contaminated respiratory equipment)	Age ≥60 years; presence of comorbidities; impaired immune system; recent hospitalization	Impaired swallowing; impaired consciousness; increased chance of gastric contents reaching the lung; impaired cough reflex

CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia

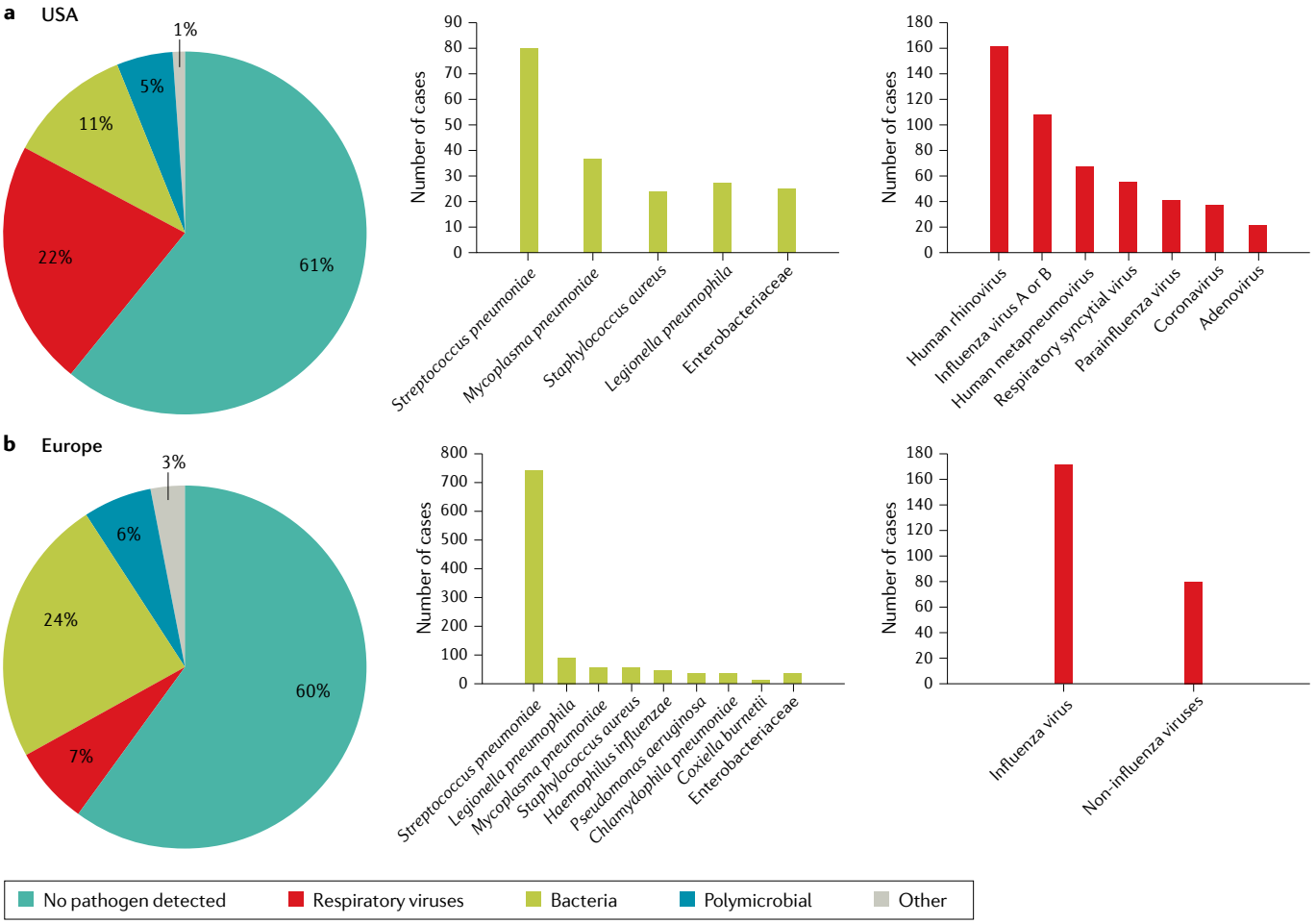

Fig. 1 | **Prevalence of microbial aetiologies of CAP in the USA and Europe. a** | Aetiology of community-acquired pneumonia (CAP) in the adult population in the USA from 2010 to 2012 (from 2,488 cases)[9]. **b** | Aetiology of CAP in the adult population in Europe from 2003 to 2014 (from 3,854 cases)[6]. Possible reasons that may explain the challenge in identifying the aetiology of pneumonia include difficulty in obtaining samples from the lower respiratory tract, the effect of antibiotic use prior to sample collection and low sensitivity of some diagnostic tests.

Microbial aetiology

Knowledge of pathogens associated with pneumonia is crucial to provide more targeted empiric antibiotic therapy, prevent the emergence of antimicrobial resistance through selection pressure and reduce health-care-associated costs.

CAP. The microbial aetiology of CAP differs by its severity at clinical presentation and by season[2,56–58]. However, the microbial aetiology of CAP is not detected in ~50% of patients; possible reasons include the failure to obtain a respiratory sample adequate for culture or before the initiation of antibiotic therapy and the inconsistent availability of newly improved molecular tests[59]. *S. pneumoniae* remains the most frequent pathogen in CAP, although a study in North America found that its incidence has decreased owing to the introduction of polysaccharide vaccines[60] and a reduced smoking rate[61,62]. No such decrease has been observed in Europe[2,63–65] (FIG. 1).

In a small proportion of patients, CAP is caused by MRSA and antibiotic-resistant gram-negative bacteria (for example, *P. aeruginosa* and *Klebsiella pneumoniae*)[2,66]. As antibiotic resistance complicates clinical management, clinicians need to recognize risk factors for these pathogens and initiate adequate empirical therapy in response (BOX 3). The main risk factors for multidrug-resistant (MDR) pathogens in CAP include immunosuppression, previous antibiotic use, prior hospitalization, use of gastric acid-suppressing agents, tube feeding and non-ambulatory status[67]. Various scoring systems can help to determine the risk of infection by antibiotic-resistant pathogens.

The *P. aeruginosa*, extended-spectrum β-lactamase (ESBL)-positive Enterobacterales and MRSA (PES) score[68] is based on several risk factors, including age 40–65 years and male sex (one point each), age >65 years, previous antibiotic use, chronic respiratory disorder and impaired consciousness (two points each), and chronic renal failure (three points). The PES score has been validated in general wards, ICUs and a very old population (age ≥80 years). One study[69] demostrated that there is an 80% probability of detecting a PES pathogen with the PES score, demonstrating good accuracy of the score. In another study[70], the accuracy of the PES score in patients of ≥80 years of age with CAP was ~64%, highlighting differences in clinical characteristics of

this population who are more susceptible to infections, recurrent pneumonia and sepsis.

The drug resistance in pneumonia (DRIP) score[71] is based on both major and minor risk factors. Major risk factors (two points each) include previous antibiotic use, residence in a long-term care facility, tube feeding and prior infection by a drug-resistant pathogen (within the past year). Minor risk factors (one point each) include hospitalization within the previous 60 days, chronic pulmonary disease, poor functional status, gastric acid suppression, wound care and MRSA colonization (within the past year).

The use of new diagnostic molecular techniques has led to an increased interest in the role of respiratory viruses as potential aetiological agents in CAP. Recent studies have reported that respiratory viruses account for 7–36% of CAP cases with a defined microbial aetiology[13,72,73]. A recent study from China reported that in patients with viral CAP, influenza virus, non-influenza virus and mixed viral infections were the cause of CAP in 63%, 27% and 10% of patients, respectively (FIG. 2). The outcomes were similar between patients with CAP due to influenza virus and those with CAP due to non-influenza viruses, although in patients with CAP due to non-influenza viruses the incidence of complications was higher[74]. In another study, 3% of all patients with a diagnosis of CAP admitted to the emergency department had pure viral sepsis[75]. Viral sepsis was present in 19% of those admitted to ICU, and sepsis was present in 61% of all patients with viral CAP.

Respiratory viruses are detected in more than half of children with CAP[76]. Respiratory viruses were the most frequent cause of pneumonia (66%) in children with an aetiological diagnosis in the USA, with respiratory syncytial virus, rhinovirus and metapneumovirus being the most common ones[76]. Bacterial pathogens were the cause of CAP in 8% of patients, with *S. pneumoniae* and *S. aureus* being the most common bacteria. Bacteria–virus co-infections were detected in 7% of patients.

HAP. Data on microbial aetiology of HAP have mostly been obtained from patients with VAP. However, studies in patients with HAP or VAP with known microbial aetiology have shown that both HAP and VAP have similar microbial aetiology, with *P. aeruginosa* and *S. aureus* being the most frequent pathogens. Other pathogens such as *Acinetobacter* spp. and *Stenotrophomonas* spp. are more frequently reported in VAP[4,77].

Antibiotic resistance is the main concern with HAP and VAP. Assessing risk factors for MDR organisms (resistant to at least one agent in three or more groups of antibiotics), extensively drug-resistant organisms (XDR; resistant to one or more agents in all but one or two antibiotic groups) and pandrug-resistant organisms (resistant to almost all groups of approved antibiotics) is central to managing patients with these pathogens[78]. In general, we can classify the risk into three categories: (1) local epidemiology (for example, ICU with high rates of MDR pathogens); (2) patient risk factors (including structural pulmonary diseases (for example, bronchiectasis), antibiotic use during the 90 days prior to HAP or VAP onset, hospitalization (2–5 days) during the 90 days prior to HAP or VAP onset, septic shock at VAP onset, acute respiratory distress syndrome (ARDS) preceding VAP, at least 5 days of hospitalization prior to VAP onset, and acute renal replacement therapy prior to VAP onset)[42]; and (3) previous colonization or infection with MDR pathogens[42]. Anaerobes and gram-negative bacilli (for example, *E. coli*, *K. pneumoniae* and *P. aeruginosa*) are the most frequent microorganisms found in aspiration pneumonia[1].

Box 3 | **Pathogen-specific risk factors**

- *Streptococcus pneumoniae*: Dementia, seizure disorders, congestive heart failure, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), HIV infection, overcrowded living conditions and smoking
- *Legionella pneumophila*: Smoking, COPD, compromised immune system, travel to outbreak areas, residence in a health-care facility and proximity to cooling towers or whirlpool spas
- MRSA: Previous MRSA infection or colonization, residence in a nursing home or long-term care facility and prior hospitalization within the previous 90 days
- *Pseudomonas aeruginosa*: Pulmonary comorbidity
- Enterobacterales: Residence in a nursing home

MRSA, methicillin-resistant *Staphylococcus aureus*

Mechanisms/pathophysiology

From colonization to infection

The mechanisms that drive LRTIs have become increasingly known. Most instances of bacterial pneumonia are caused by microorganisms that translocate from the nasopharynx to the lower respiratory tract[79,80]. Bacteria enter the nasopharynx after shedding from a colonized individual. Pathogens can spread between individuals via direct or indirect contact, droplets and aerosols[81]. Transmission success depends on many variables, including environmental conditions, gathering of people and host factors, such as the distribution of pattern recognition receptors in the epithelial cells of the airways[81]. Pathogen adherence to the upper airway epithelium is a crucial first step in colonization and subsequent infection. Once in the nasopharynx, bacteria escape from mucus and attach to the epithelium using multiple strategies to evade host clearance, including expression of host-mimicking or antigenically varying molecules[82] (that is, molecules that imitate the structure of host molecules or can vary their antigens to avoid recognition by host immune cells). Microorganisms gain entry to the lower airways through inhalation or, less frequently, by pleural seeding from blood. Selection of colonizing mutants that can evade immune clearance is considered to precede infection[79]. Infection occurs when host defences are impaired and/or there has been exposure to a highly virulent microorganism or a large inoculum. Several factors can facilitate the transition from colonization to infection, including preceding viral infection and chronic lung diseases. Other mechanisms involved in the increased susceptibility to infection include loss of barrier integrity and impaired host

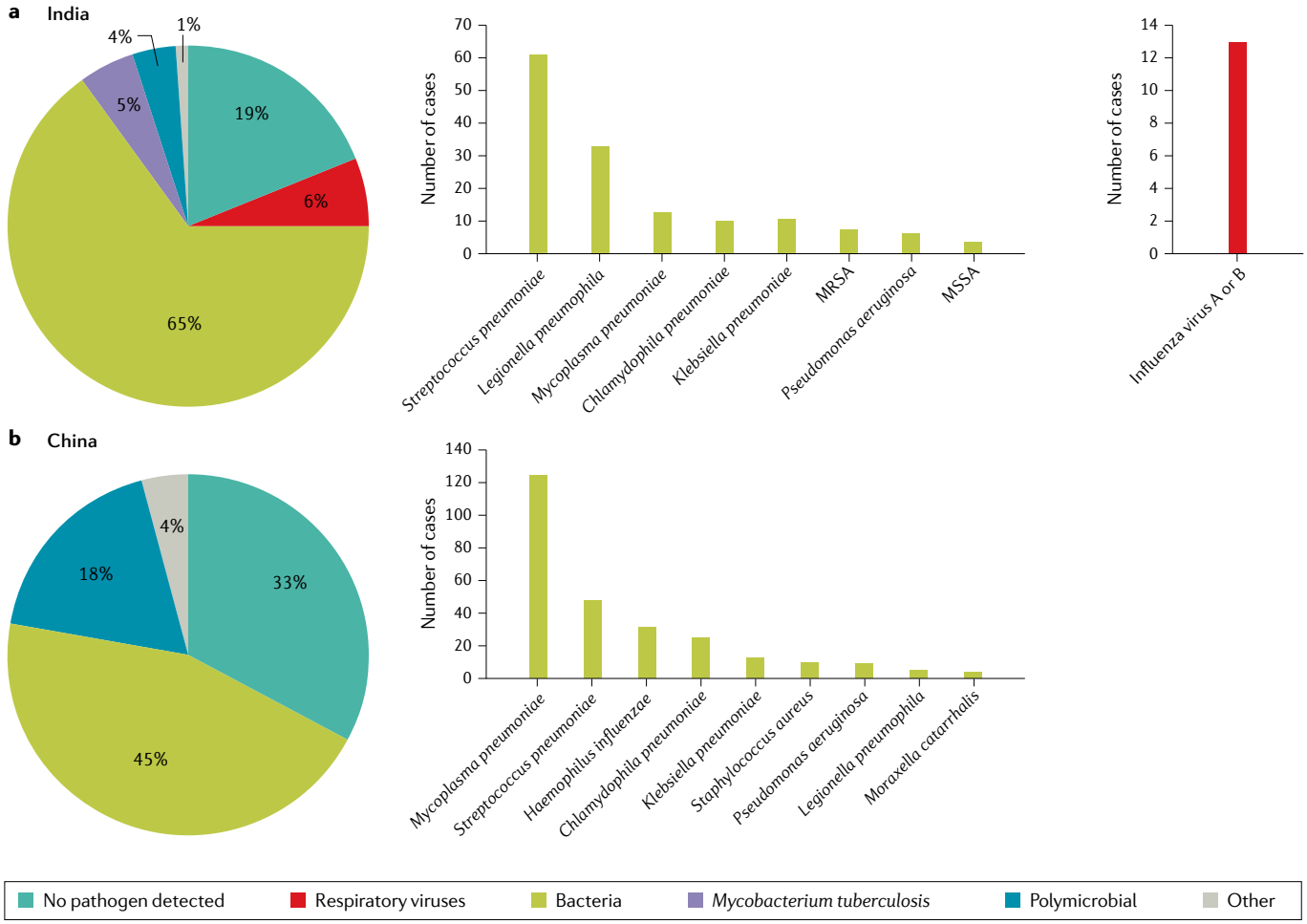

Fig. 2 | **Prevalence of microbial aetiologies of CAP in India and China. a** | Aetiology of community-acquired pneumonia (CAP) in the adult population in India from 2013 to 2015 (from 225 cases)[54]. **b** | Aetiology of CAP in the adult population in China from 2004 to 2005 (from 593 cases)[55]. Possible reasons that may explain the challenge in identifying the aetiology of pneumonia include difficulty in obtaining samples from the lower respiratory tract, the effect of antibiotic use prior to sample collection and low sensitivity of some diagnostic tests. MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

defences due to complex interactions amongst anatomical structures, microorganisms (and their virulence factors) and the host immune system[79,80,83].

Of note, it has become clear that healthy lungs are not sterile; instead, they harbour a unique microbiota that includes ~100 different taxa[84]. The main genera in healthy lower airways are *Prevotella*, *Streptococcus*, *Veillonella*, *Fusobacterium* and *Haemophilus*[84]. The pathogenesis of pneumonia has been suggested to include a change in the lung microbiota, from a physiological, homeostatic state to dysbiosis, in association with a low microbial diversity and high microbial burden, and with corresponding immune responses[84,85] To further support this concept, longitudinal lung microbiota studies are required to document transitions from homeostatic to dysbiotic states during the development and resolution of pneumonia. An additional area of research lies in analysing the virome and mycobiome in airways and their influence on host defence against pneumonia. The mechanisms by which lung microbiota affect immunity in the airways have been partially elucidated. Bacteria present in the upper airways that potently stimulate nucleotide-binding oligomerization domain-containing (NOD)-like receptors (*Staphylococcus aureus* and *Staphylococcus epidermidis*) increase resistance to pneumonia through NOD2 and induction of release of granulocyte–macrophage colony-stimulating factor[86].

Mechanisms of infection. A general mechanism of infection of the lower airways is difficult to define. The many different microorganisms that can cause pneumonia do not seem to express specific features. Even in specific populations (for example, young children, hospitalized patients, older individuals), a spectrum of pathogens, rather than a specific microorganism, can cause pneumonia. This finding has led to the assumptions that the development of pneumonia largely depends on the host response to the microbe in the airways, with pathogen characteristics playing a less prominent role[83]. Nonetheless, virulence factors expressed by microorganisms do contribute to the ability of specific pathogens

to cause pneumonia[79,80]. For example, pneumolysin, a virulence factor expressed by *S. pneumoniae*, is a member of the cholesterol-dependent cytolysin family that can form large pores in (and thereby injure) eukaryotic cells with cholesterol-containing membranes[87]. *S. aureus* expresses several virulence factors, such as α-haemolysin (also known as α-toxin), a pore-forming toxin that causes cell death via activation of the inflammasome[88]. α-Haemolysin binds to the disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) and results in disruption of the barrier function of the respiratory epithelium[88]. Finally, toxins secreted by the type III secretion system are a key element in *P. aeruginosa* virulence in the lung. Genes encoding type III-secreted toxins are induced in *P. aeruginosa* upon contact with host cells, eliciting a plethora of effects, including cytotoxicity[89].

Once an LRTI has occurred, the maintenance of lung homeostasis whilst in the presence of microbes depends on an adequate balance between two seemingly opposing processes, immune resistance and tissue resilience, that are largely mediated by the same cell types. Whilst immune resistance seeks to eliminate invading microbes, tissue resilience strives to prevent or resolve tissue damage caused by the immune response, the pathogen or both[83]. The organized actions of immune resistance and tissue resilience determine whether and how an LRTI progresses or resolves. Inadequate or unfitting immune responses can result in adverse outcomes, such as ARDS, defined as the acute onset of non-cardiogenic pulmonary oedema, hypoxaemia and the need for mechanical ventilation[90,91]. Unbalanced immune responses during pneumonia can also result in extrapulmonary complications, some of which can occur up to years after the respiratory illness (see below).

Immune resistance

Anatomical barriers present the first line of defence against pneumonia. Mucociliary clearance, mediated by mucous and liquid layers and cilia on the surface of respiratory epithelial cells, is considered the primary innate defence mechanism[92]. The respiratory epithelium produces a robust barrier composed of secretory products, surface glycocalyces and membranes, and intercellular junctional proteins linked to the actin cytoskeleton[92]. Cell-associated and secreted mucins form a polymeric glycoconjugate layer that can bind and transport pathogens from the airways[92]. The branching bronchial tree provides an additional defence mechanism by preventing particles of >3 μm in diameter from entering the lower airways[92]. If microbes do reach the lower respiratory tract, the host defence becomes shaped by an interplay between resident and recruited immune cells and mechanisms (FIG. 3).

Innate immunity. Various innate immune cells reside in quiescent airways to provide the next line of defence against pathogens. Lung epithelial cells can be triggered through a variety of receptors that recognize not only pathogens but host-derived molecules as well, including damage-associated molecular patterns (released upon cell injury) and cytokines. Many pattern recognition receptors (for example, toll-like receptors) then induce nuclear factor κB, which is a major driver of protective immunity in the epithelium[93,94]. In the alveoli, surfactant proteins SP-A and SP-D produced by type II epithelial cells can directly inhibit microbes[95]. Recently, G-protein-coupled bitter taste receptors (T2R) and sweet taste receptors (T1R) were identified in respiratory epithelial cells[96]; bacterial quorum-sensing molecules can trigger bitter taste receptors, whilst sugars can activate sweet receptors, and these interactions may then modify host defence mechanisms[97]. IL-17 and IL-22 mediate protection during pneumonia largely through epithelial cell activation[98]. IL-17 stimulates the epithelium to secrete antimicrobial proteins and CXC chemokines that trigger neutrophil recruitment. The protective properties of IL-22 are linked to its function in stimulating epithelial cell proliferation, which is indispensable for repair following injury[99].

Alveolar macrophages (AMs), which reside on lower airway surfaces, have essential roles in both immune resistance and tissue resilience[100]. During homeostasis, they limit the effect of potentially noxious environmental stimuli through anti-inflammatory effects. The crucial role of AMs in immune resistance during pneumonia is illustrated by studies showing impairment of the host defence when AM function is disrupted[94]. Microbes can activate AMs via several pattern recognition receptors and nuclear factor κB, leading to the production of pro-inflammatory cytokines that orchestrate subsequent, innate immune responses necessary for resistance. In addition, stimulated by AM apoptosis, activated AMs can phagocytose and kill pathogens[101]. By contrast, AM death via non-apoptotic pathways, such as necroptosis, impairs antibacterial defence during pneumonia[102]. The complex role of necroptosis in the host response to bacterial infection is illustrated by reports linking necroptosis to exaggerated inflammation and impaired bacterial clearance during *S. aureus* pneumonia[103], whereas it has a protective, anti-inflammatory effect associated with improved bacterial clearance during systemic *S. aureus* infection[104]. Local conditions may instruct AMs in providing the most suitable response.

Innate lymphoid cells (ILCs) serve as counterparts to T cells by regulating immune responses via the production of effector cytokines and by influencing functions of other innate and adaptive immune cells[105]. These cells are especially abundant on the mucosal surfaces of the lung. There are three major groups of ILCs, namely, ILC1, ILC2 and ILC3. ILC classification reflects these cells' capacity to secrete types 1, 2 and 17 cytokines, respectively. Beneficial roles for ILC1s and ILC2s have been reported in viral pneumonia models[106,107]; lung ILC3s have a protective role in pneumonia by secreting IL-17 and IL-22 (REFS[108,109]). Mucosal-associated invariant T cells are other innate-like T lymphocytes that are abundant in the lung mucosa[110]. These cells probably have a role in protective immunity during airway infection through a variety of mechanisms, including production of pro-inflammatory cytokines, macrophage activation and recruitment of effector helper and cytotoxic T cells[111].

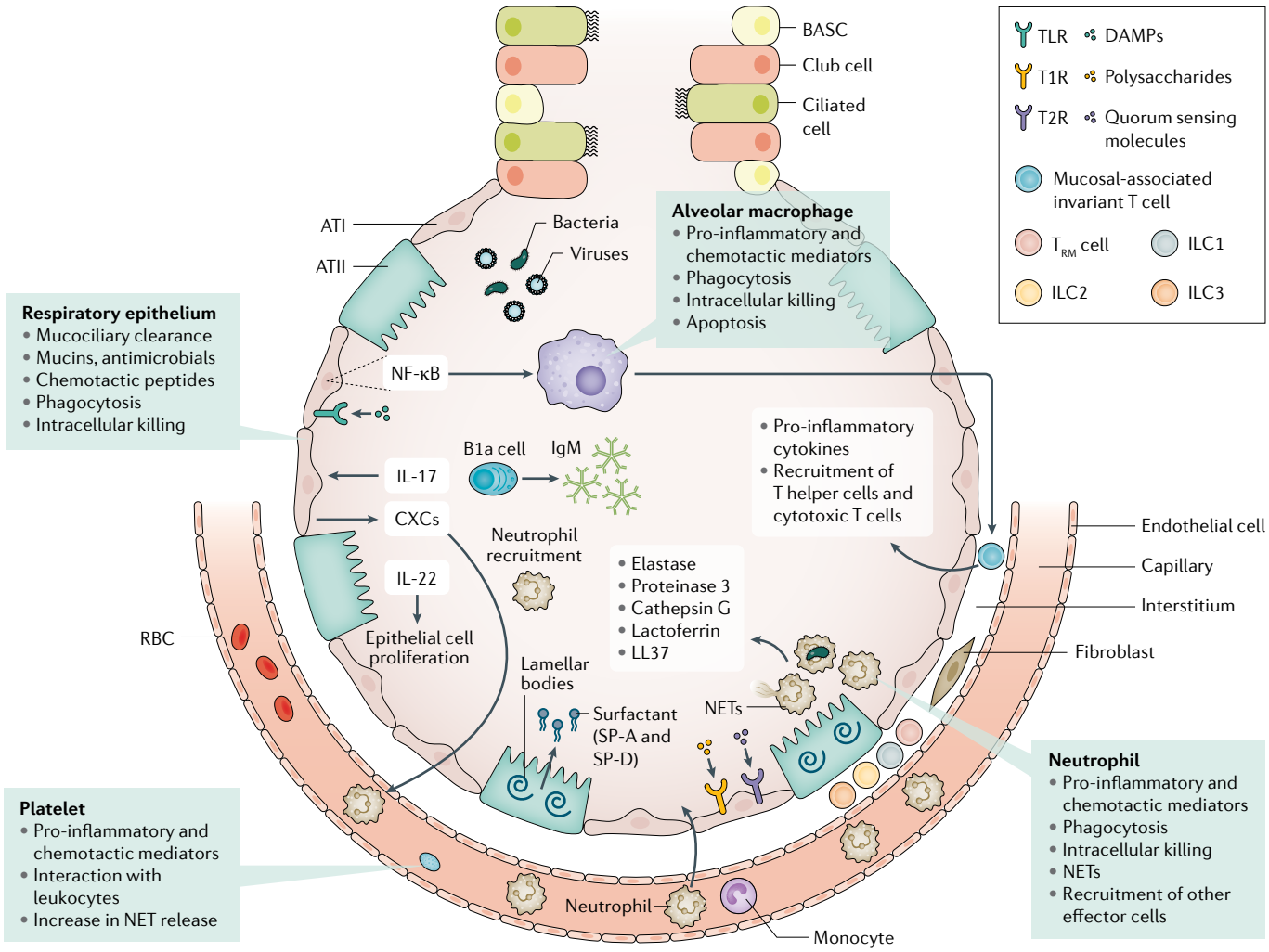

Fig. 3 | **Immune resistance.** Immune resistance aims to eradicate microorganisms that invade the airways. Respiratory epithelial cells are covered by cell-associated and secreted mucins that form a layer of polymeric glycoconjugates that remove pathogens from the airways. The epithelium can also remove pathogens through phagocytosis and intracellular killing. The quiescent alveolar space contains many alveolar macrophages that, upon activation, can phagocytose and kill pathogens, which is improved by apoptosis. Innate lymphoid cells (ILCs) are tissue-resident cells populating the pulmonary mucosa. Together with natural killer cells, ILCs boost host defence during airway infection. Neutrophils migrate to the airways attracted by chemotactic proteins released by respiratory epithelial cells and alveolar macrophages; these chemotactic proteins also promote the recruitment of other leukocyte subsets. The lung contains a marginated pool of neutrophils tethered to the vasculature, enabling rapid neutrophil recruitment into tissue upon infection. Adequate pulmonary immunity entails neutrophil-mediated killing of invading microbes by several effector mechanisms, including the release of neutrophil extracellular traps (NETs). Platelets can form complexes with leukocytes, facilitating NET formation and the release of microbicidal agents. Resident memory T (T_{RM}) cells are generated after exposure to pathogens and reside in the quiescent lung. ATI, alveolar type I cell; ATII, alveolar type II cell; BASC, bronchioalveolar stem cell; CXCs, CXC chemokines; DAMPs, damage-associated molecular patterns; NF-κB, nuclear factor-κB; RBC, red blood cell; SP, surfactant protein; T1R, G-protein-coupled sweet taste receptor; T2R, G-protein-coupled bitter taste receptor; TLR, Toll-like receptor.

When resident cells are unable to eradicate invading pathogens, mechanisms are activated to attract additional effector cells to the site of infection. Neutrophils are the first and most profusely recruited cells in response to infection[112]. Primed neutrophils have a strongly increased capacity to phagocytose microbes and initiate a respiratory burst response[112]. In addition, neutrophil products, such as elastase, proteinase 3 (also known as myeloblastin), cathepsin G, lactoferrin and LL-37, exert potent antimicrobial activities[113]. Neutrophil extracellular traps, comprising decondensed chromatin fibres that carry histones and antimicrobial peptides, are also released to kill pathogens[113]. The crucial role of neutrophils in pulmonary immune resistance is illustrated by the increased susceptibility found in patients with neutropenia or neutrophil deficiencies and mouse pneumonia models, in which neutrophil depletion has been shown to exacerbate infection with several pathogens[112]. In addition to AMs, newly recruited inflammatory monocytes–macrophages are involved in immune resistance during pneumonia[114]. In mice, induction of *K. pneumoniae*-associated pneumonia has been found to lead to the recruitment of inflammatory monocytes to the lungs where they mediate the influx of protective ILCs producing IL-17 through the release of tumour necrosis factor[109]. Innate-like B1 B cells mainly

reside in the pleural space. In response to infection, B1a B cells migrate to the lung parenchyma to produce polyreactive immunoglobulin M and contribute to protective immunity[115]. Platelets also provide immune resistance during pneumonia through various mechanisms, including platelet–bacteria interactions and complex formation with leukocytes. Other mechanisms include facilitating neutrophil extracellular trap formation and stimulating the release of microbicidal agents that can directly lyse bacteria[116]. Thrombocytopenia is associated with impaired antibacterial defence during murine pneumonia[117,118].

Finally, several distant organs can affect immune resistance in the respiratory tract. For example, depletion of gut microbiota by broad-spectrum antibiotics has been shown to impair host defence during viral and bacterial pneumonia in mice[119,120]. This protective gut–lung axis has been hypothesized to be mediated, at least in part, by gut-derived microbial products that can improve host defence mechanisms in other tissue[121]. The existence of a liver–lung axis has been suggested in many studies; pneumonia elicits a robust acute-phase protein response in the liver, probably mediated by cytokines released into circulation, and distinct acute-phase proteins can improve antibacterial defence through several mechanisms, for example, by enhancing opsonophagocytosis (phagocytosis mediated by opsonins) and respiratory burst activity by immune cells and by limiting iron availability to bacteria.

Adaptive immunity. Previous encounters with respiratory pathogens shape memory defence mechanisms against pneumonia. Evidence highlights roles of innate immune cells (for example, epithelial cells and AMs) that had been modified by a prior infection to trigger epigenetic alterations in a so-called process of 'trained immunity'[122]. Trained immunity has received attention within the context of pneumonia in humans. The Bacille Calmette–Guérin vaccination induces trained immunity. When administered to older patients after hospital discharge, the vaccination increased time to first infection, and most of the protection was observed against respiratory tract infections of probable viral origin[123]. Humoral response to microbes improves host defence by producing pathogen-specific antibodies, as illustrated by the efficacy of vaccines in diminishing the risk of pneumonia.

The airways contain pools of memory cells that are assembled in tertiary lymphoid organs in the upper airways and in bronchus-associated lymphoid tissue in the lower airways. Together, these cells protect against infection through local and systemic antibody production[124]. The majority of $CD4^+$ T cells and $CD8^+$ T cells in the quiescent lung have a memory phenotype (hence they are named resident memory T (T_{RM}) cells) and are generated in response to exposure to respiratory pathogens[125]. In experimental mouse models, the lung is enriched with T_{RM} cells specific for multiple viral and bacterial pathogens following a respiratory infection, and these cells contribute to future protective immunity. For example, lobar pneumococcal pneumonia in mice leads to the accumulation of $CD4^+$ T_{RM} cells in the infected lobe, but not in other areas of the lung. This T_{RM} cell-populated lobe expresses better defence against reinfection by *S. pneumoniae* than other lobes[126].

Tissue resilience

Tissue resilience is essential in controlling excessive inflammation whilst sustaining effective protection against microbes (FIG. 4). AMs contribute to tissue resilience by producing anti-inflammatory cytokines, such as IL-10 and IL-1 receptor antagonist, and through the phagocytosis of apoptotic leukocytes. This process is named efferocytosis and protects tissue in two manners: by preventing the release of pro-inflammatory and toxic contents from dying cells and by concurrently prompting the release of anti-inflammatory and repair factors, including transforming growth factor β1, prostaglandin E_2, and pro-resolving lipid mediators[100]. Pro-resolving lipid mediators (resolvins, protectins and maresins) can mediate a large variety of immune responses in pneumonia, both increasing bacterial killing and promoting tissue repair[127]. Such mediators have been shown to have important protective roles in mouse models of bacterial pneumonia[128,129].

The structural integrity of the epithelial barrier in the respiratory tract is crucial to tissue resilience. Contributors to epithelial resilience include β-catenin (also known as catenin β1)[130], forkhead box protein M1 (FOXM1)[131], tumour protein 63 (p63)[132] and signal transducer and activator of transcription 3 (STAT3)[133,134]. Interestingly, a deficiency of STAT3 in airway epithelial cells results in exaggerated lung injury during experimental pneumonia[133,134]. Epithelial cell-derived leukaemia inhibitory factor (LIF) has been implicated as an important inducer of STAT3 in the respiratory epithelium, and inhibition of LIF has been shown to increase lung injury in pneumonia[135]. Several immune cells recruited to the site of infection during pneumonia are known to contribute to tissue resilience, including myeloid-derived suppressor cells[136], regulatory T cells[137], ILC2s[138] and natural killer cells[139,140].

Lung pathology

With respect to the histopathology of bacterial pneumonia, four stages have classically been described: congestion, red hepatization, grey hepatization and resolution (FIG. 5). The term hepatization refers to an increased firmness of inflamed lung tissue that renders the tissue consistency similar to that attributed to hepatic tissue. In the early stages of bacterial pneumonia, lung tissue shows mild intra-alveolar oedema and congestion of the capillaries within the alveolar septa[141]. This stage is followed by inflammatory exudation with an accumulation in the alveolar spaces of neutrophils, red blood cells and fibrin, and a subsequent, gradual disintegration of red blood cells and neutrophils. The exudates are eventually transformed into intra-alveolar fibromyxoid moulds, consisting of macrophages and fibroblasts, and gradual resolution follows thereafter.

Viral pneumonia is typically associated with interstitial inflammation and diffuse alveolar damage[142]. Interstitial inflammation involves the alveolar walls, which widen and usually contain an inflammatory

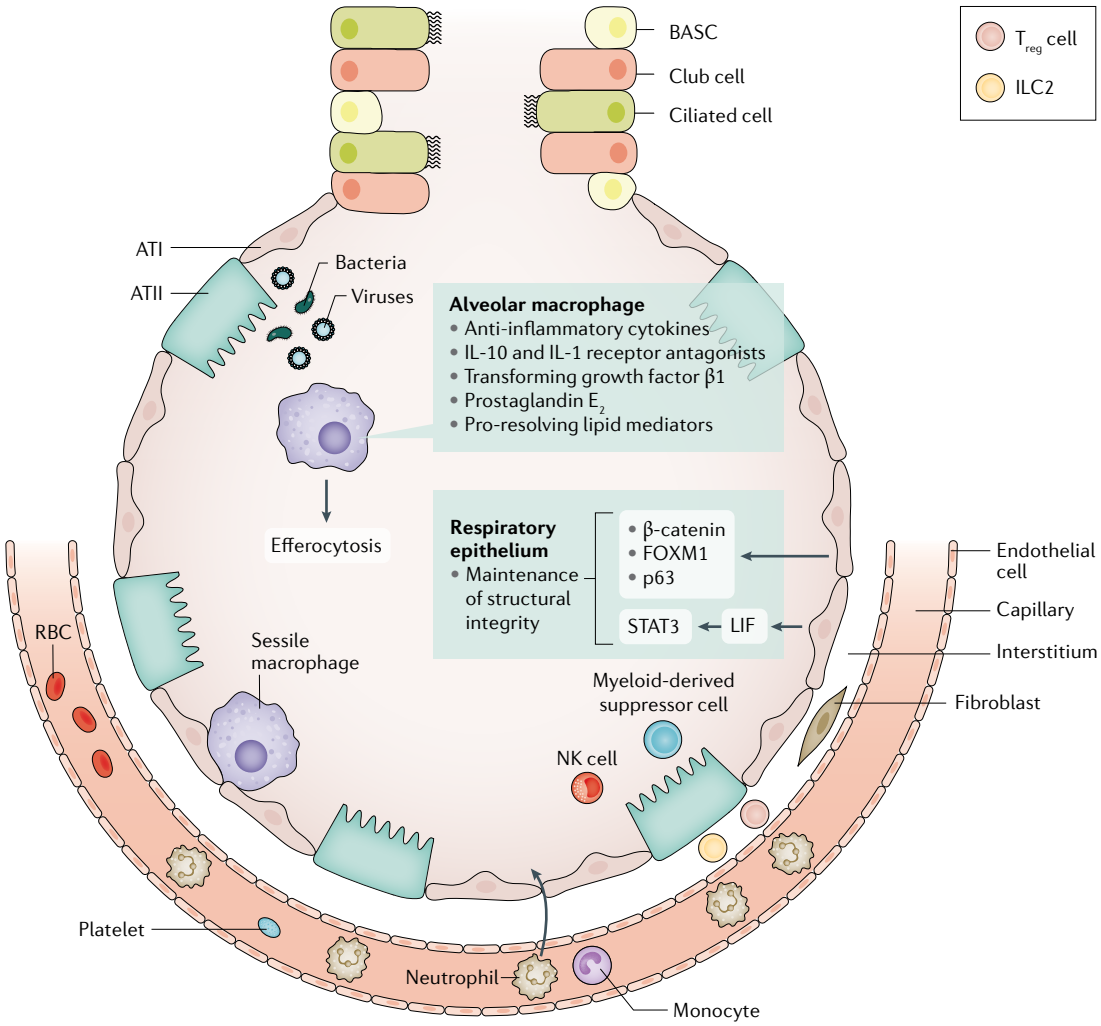

Fig. 4 | **Tissue resilience.** Tissue resilience controls excessive inflammation whilst safeguarding protection against pathogens. The respiratory epithelium is an important player in tissue resilience. Maintenance of the structural integrity of the epithelial barrier is a crucial factor here. Alveolar macrophages also have an important role, via release of anti-inflammatory mediators and efferocytosis (phagocytosis of apoptotic leukocytes). Sessile macrophages adhere to the epithelium, where they probably contribute to tissue resilience. Cell types recruited to the site of infection during pneumonia that are involved in tissue resilience include myeloid-derived suppressor cells, regulatory T (T_{reg}) cells, type 2 ILC2s and natural killer (NK) cells. ATI, alveolar type I cell; ATII, alveolar type II cell; BASC, bronchioalveolar stem cell; FOXM1, forkhead box protein M1; ILC, innate lymphoid cell; LIF, leukaemia inhibitory factor; RBC, red blood cell; STAT3, signal transducer and activator of transcription 3.

infiltrate of lymphocytes, macrophages and plasma cells in some cases. Alveolar damage is characterized by pink hyaline membranes lining the alveolar septa that follow a pattern of organization and resolution similar to that of intra-alveolar inflammation in bacterial pneumonia.

In addition to these features, specific microorganisms may cause different histopathological changes such as granulomas, multinucleated giant cells or specific viral inclusions.

Extrapulmonary complications

Extrapulmonary complications are extremely common in patients with pneumonia, including those without sepsis. Such complications entail both acute and long-term adverse sequelae. Patients who have been hospitalized for pneumonia have higher rates of all-cause hospitalization and an increased mortality risk for 10 years after discharge[35] compared with matched patients hospitalized for other pneumonia-unrelated conditions.

Sepsis. Sepsis, defined as a life-threating organ dysfunction caused by a dysregulated host response to an infection[143], is most often caused by pneumonia (up to half of all patients with sepsis)[144]. Conversely, of patients who are hospitalized with CAP[145] or HAP[146], 36% and 48% have been reported to develop sepsis, respectively. Both pro-inflammatory and anti-inflammatory reactions characterize host response to sepsis, which varies strongly between individuals. Pro-inflammatory responses include the release of cytokines, activation of the complement and coagulation system (which could

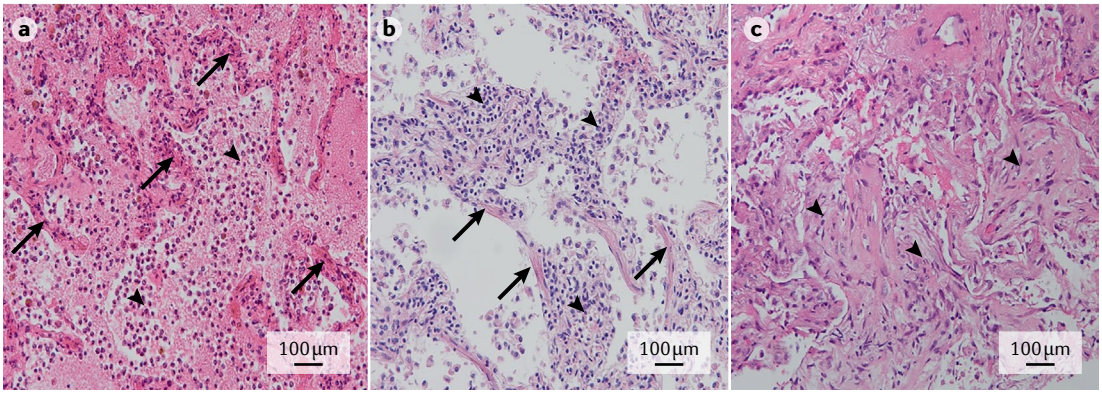

Fig. 5 | **Histology of pneumonia. a** | Early stage bacterial pneumonia, with congestion of septal capillaries (arrows) and intra-alveolar presence of oedema, neutrophils and a meshwork of fibrin strands (arrowheads). **b** | Early stage viral pneumonia, with interstitial lymphocytic infiltrates (arrowheads) and diffuse alveolar damage, as evidenced by the presence of hyaline membranes (arrows). **c** | Organizing pneumonia, with intra-alveolar fibroblast plugs (arrowheads) and few remnant fibrin deposits. Haematoxylin and eosin staining; original magnification ×20. Images in parts **a**–**c** courtesy of J.J.T.H. Roelofs, Amsterdam UMC, Netherlands.

result in disseminated intravascular coagulation), and disruption of the normal barrier and anticoagulant function of the vascular endothelium. Anti-inflammatory responses can result in immune suppression, in part due to apoptotic loss of lymphoid cells[147,148].

Cardiovascular disease. Pneumonia particularly affects the cardiovascular system, and its effects include depression of left ventricular function, myocarditis, arrhythmias, ischaemia and infarction[149]. Patients hospitalized for pneumonia have an increased short-term and long-term risk (up to ten years) of cardiovascular disease[150]. A meta-analysis of the incidence of cardiac events within 30 days of pneumonia diagnosis found new or worsening heart failure in 14% of all patients, new or worsening arrhythmias in 5% and acute coronary syndromes in 5%[151]. Approximately 90% of cardiac complications occur within 7 days of a pneumonia diagnosis, and more than half occur within the first 24 h[149]. In a multicentre study, one third of patients hospitalized for CAP experienced intrahospital cardiovascular events, mainly involving the heart, and such occurrence was associated with a fivefold increase in 30-day mortality. Independent risk factors for cardiovascular events were severity of pneumonia and pre-existing heart failure[152]. Additionally, hospitalization for pneumonia is associated with an increased risk of new-onset heart failure in the intermediate and long term, with a hazard ratio of 2 after 5 years[34]. In patients with pneumonia who require ICU treatment within 24 h of hospital admission, approximately half have diagnostic criteria for myocardial infarction[153]; cardiac complications are the direct or main cause of death in 27% of patients hospitalized for pneumonia[154]. Notably, whilst the increased risk for myocardial infarction associated with pneumonia is proportional to disease severity, it is not restricted to patients with pneumonia-induced sepsis[155]. Even mild respiratory infection is associated with an increased risk of myocardial infarction for several months after the onset of infection[155].

The mechanisms underlying an increased risk of cardiovascular disease after pneumonia are probably multifactorial. Hypoxaemia due to impaired gas exchange and ventilation–perfusion mismatching, as well as endothelial dysfunction causing vasoconstriction, may increase vulnerability to ischaemic events[149]. Systemic inflammation during pneumonia can increase inflammatory activity within coronary atherosclerotic plaques, rendering them prone to rupture[149]. The systemic host response during pneumonia also entails endothelial dysfunction and procoagulant changes, which can promote thrombus formation at the site of a ruptured coronary plaque[149]. Indeed, as reflected by elevated markers of coagulation activation in the circulation, the majority of patients admitted to hospital for pneumonia have a procoagulant phenotype[156,157].

Patients with pneumonia and acute coronary syndromes show higher platelet-aggregating activity than patients with acute coronary syndromes without pneumonia[149]. Notably, the connection between pneumonia and cardiovascular disease is probably bidirectional. For example, pre-existing heart failure is a risk factor for pneumonia, perhaps partially related to impaired immune responses[149]. Preclinical investigations suggest that lung congestion can facilitate the growth of common respiratory pathogens in the airways[149]. With regard to long-term risk, investigations in mice predisposed to developing atherosclerosis[158] and post mortem examinations in humans[159] have suggested that infection can elicit pro-inflammatory responses in atherosclerotic lesions and result in increased vulnerability for coronary and cerebrovascular events. For example, acute lung inflammation induced by intratracheal administration of lipopolysaccharide in mice prone to atherosclerosis resulted in destabilization of atherosclerotic plaques; neutrophil depletion prevented this destabilization, suggesting a role for neutrophils in plaque weakness elicited by lung injury[160]. In addition, systemic inflammation and coagulation are sustained in many patients with pneumonia and have been associated with an increased risk of cardiovascular death[161,162]. Left ventricular dysfunction during pneumonia may be

secondary to depressant activity of pro-inflammatory cytokines in circulation and/or altered vascular reactivity[149].

Other complications. Additional extrapulmonary complications of pneumonia include a decline in cognition and functional status[163,164]. Pneumonia is associated with a 57% increase in the risk of dementia[164]. Encephalopathy associated with acute infectious disease has been studied in the context of sepsis[165,166]. Mechanisms involved include impaired circulation in the brain secondary to hypotension, a disturbed vasoreactivity, endothelial dysfunction and microvascular thrombosis, which can result in ischaemic and haemorrhagic lesions. The blood–brain barrier can be disturbed through increased activity of pro-inflammatory cytokines and reactive oxygen species produced at least in part by astrocytes. Activation of microglia can further contribute to neuronal damage in the brain[166].

Approximately one fifth of patients hospitalized with pneumonia are readmitted to the hospital within 30 days; pneumonia, cardiovascular disease and (chronic obstructive) pulmonary disease are the most common diagnoses[167]. An increased susceptibility for infection after pneumonia may be related to a relatively immunocompromised state, as has been described in patients with sepsis[147]. Knowledge of immunological defects contributing to recurrent pneumonia (usually defined as a new episode of pneumonia within several months of the previous one, separated by at least a 1-month asymptomatic interval and/or radiographic clearing of the acute infiltrate)[168] is limited. A small study involving 39 patients suggested that immunoglobulin deficiency and an inability to react to polysaccharide antigens are associated with an increased incidence of recurrent pneumonia[169]. Further, a study in mice found a reduced capacity of AMs to phagocytose *E. coli* and *S. aureus* following recovery from primary pneumonia, a reduction mediated by signal-regulatory protein-α (also known as tyrosine–protein phosphatase non-receptor type substrate 1) and associated with an impaired host defence after secondary infection of the lower airways[170].

Diagnosis, screening and prevention

The most common symptoms of pneumonia are cough, breathlessness, chest pain, sputum production and fatigue[171,172]. Symptoms are not a part of the initial severity assessment of patients, as the initial symptom burden does not influence outcome. Exceptions include delirium, which is associated with an increased risk of mortality[173], and pleuritic chest pain, which is associated with an increased risk of para-pneumonic effusion and complicated (infected) para-pneumonic effusion[174,175]. Usually mild disease refers to patients with CAP who do not require hospitalization, moderate disease to those cared for in conventional hospital wards, and severe disease to those admitted to the ICU.

It is not possible to differentiate bacterial and viral pneumonia based on symptoms in adults or children, as patients report similar symptoms regardless of microbial aetiology[176]. A recent study found that artificial intelligence was also unable to differentiate microbial aetiology based on symptoms, clinical features and radiology[177].

Diagnosis

CAP is usually clinically suspected in the presence of acute (≤7 days) symptoms of LRTI, such as cough, expectoration, fever and dyspnoea, as well as the presence of new infiltrates on chest radiographs (CXRs)[178]. In older patients, symptoms are typically less evident, and fever can be absent in as many as 30% of patients[179]. Symptoms may also be less evident in patients treated with steroids, NSAIDs and antibiotics[6]. Other pulmonary diseases — most frequently pulmonary embolism and lung cancer — may present with fever and pulmonary infiltrates that can mimic CAP. Interstitial and systemic diseases can also mimic CAP. When diagnosing CAP, it is extremely important to review prior chest CXRs if available, as an additional means to help rule out the disease.

Although HAP is also suspected clinically, symptoms may be hidden by either other medications or the cause of admission. No studies exist about symptom duration in HAP before diagnosis; however, it is usually suspected when patients present with pyrexia (fever) and/or tachypnoea (rapid breathing). HAP diagnosis is believed to be usually delayed, which could explain the higher mortality observed in this population than in patients with VAP.

VAP is suspected when there are at least two of the following symptoms: fever or hypothermia, leukocytosis or leukopenia, and evidence of purulent secretions in an endotracheal tube or tracheostomy[4]. For VAP diagnosis, clinicians often rely on clinical parameters; radiological and laboratory parameters help initiate antimicrobial treatment. Scores have been proposed to facilitate diagnosis. For example, the clinical pulmonary infection score (CPIS)[180] is the most common one, and it is based on points assigned to various signs and symptoms of pneumonia. A CPIS score of >6 suggests VAP, although score sensitivity and specificity are not perfect. In fact, the FDA does not accept this score to diagnose VAP in randomized controlled trials studying antibiotics. In patients with VAP, fever and pulmonary infiltrates can present as atelectasis (collapse of parts of the lung), alveolar haemorrhage and pulmonary thromboembolism, amongst other conditions. In a landmark study using immediate post mortem lung histopathology and microbiology as a gold standard, the presence of two clinical criteria plus the presence of infiltrates on CXRs had a 70% sensitivity and 75% specificity in the diagnosis of VAP [181].

Radiology. Radiographic confirmation is essential for the diagnosis of pneumonia. CXRs provide important information about the site, extent and associated features of pneumonia (for example, the lobes involved and the presence of pleural effusion and cavitation)[5] (FIG. 6). CXRs have a sensitivity and specificity of 43.5% and 93%, respectively, for detecting pulmonary opacities[182]. In CAP, sensitivity and specificity of 66% and 77%, respectively, have been reported[183] using CT scans as the gold standard. The presence of either pleural fluid

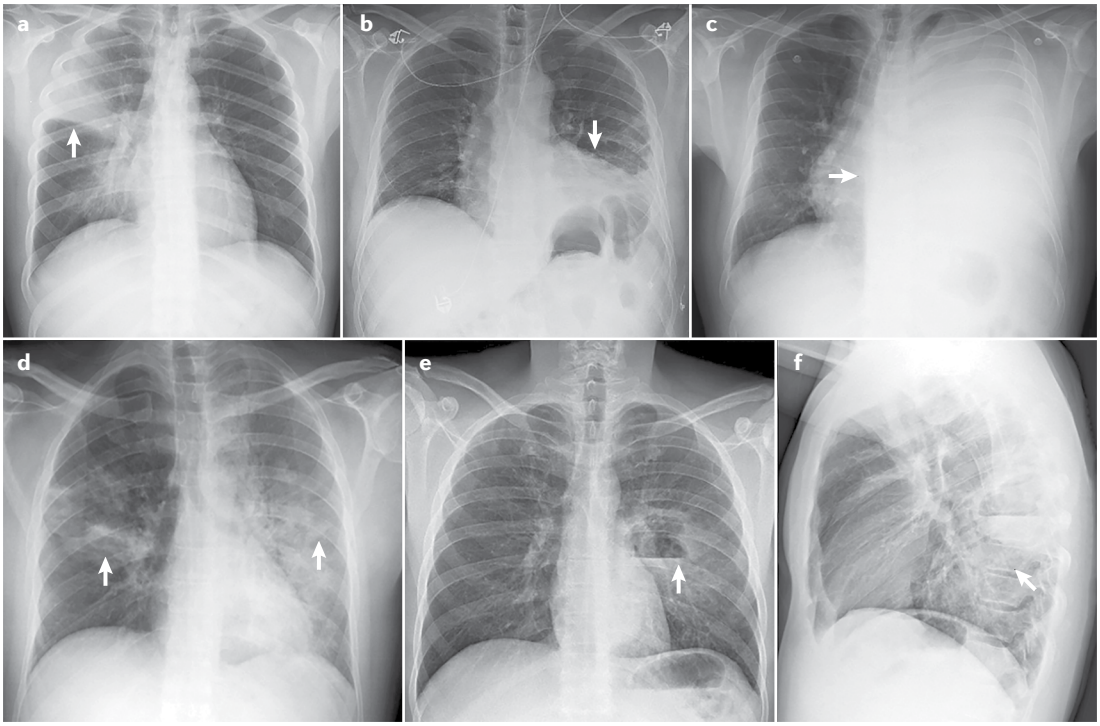

Fig. 6 | **Associated features of pneumonia on plain radiography.** Pneumonia in upper right lobe (arrow) (part **a**); pleural effusion on the left side (arrow) (part **b**); massive pleural effusion in the left lung (arrow) (part **c**); bilateral pneumonia (arrows) (part **d**); lateral image showing left parahilar cavitation with air–fluid level in the lower left lobe (arrow) (part **e**); front-to-back image in the same individual as in part **e**.

or multilobar pneumonia serve as indicators of severity[5]. In CAP, the development of pulmonary infiltrates that were not previously present on a simple posterior–anterior (PA) CXR is essential for CAP diagnosis. The standard CXR for CAP consists of a PA and lateral images; the use of lateral projection images increases diagnostic performance of PA images. In HAP, radiographic evidence of infiltrates is usually determined by CXR examination alone. In VAP, new infiltrates are usually detected by anterior–posterior projection in the supine position; however, in this situation, CXRs are insufficiently sensitive and specific.

In studies in patients hospitalized with CAP, CT identified up to 35% of patients with CAP who had not initially been caught by CXRs[184]. In many patients with COVID-19, CT scans detect pulmonary infiltrates not observed on simple CXRs[185]. In patients with CAP, CT scans serve as a practical complement to CXRs in several cases: when radiographic findings are non-specific, when pulmonary complications such as empyema (pus in the pleural space) or cavitation are present, when there is suspicion of an underlying lesion such as lung carcinoma, and when recurrent pneumonia or non-resolving pneumonia is present[186]. Although this supporting role of CT scans is assumed to apply to patients with HAP as well, supporting evidence is lacking.

Ultrasonography. Lung ultrasonography is a non-invasive imaging method that is now frequently used in many emergency departments and ICUs. Advantages over CT include the absence of radiation exposure, ready use at the bedside and reasonable diagnostic sensitivity and specificity[187]. However, the technique has a steep learning curve, especially in mechanically ventilated patients. In a systematic review, lung ultrasonography was shown to have a sensitivity of 88% and a specificity of 89%, with a ~90% probability of diagnosing pneumonia[188]. Echographic diagnosis is more complex in patients with VAP, and only a few observational studies have been conducted to date[188]. The best of these studies have shown that such diagnosis had better accuracy than the CPIS score alone; the addition of direct Gram stain examination in quantitative cultures of endotracheal aspirates further improved accuracy[189,190]. On the basis of on these results, the ventilator-associated pneumonia lung ultrasound score (VPLUS) was developed, and has a sensitivity of 71% and a specificity of 69% for VAP diagnosis[190].

Microbiology and laboratory tests. Recommendations for microbiological diagnosis in CAP vary according to disease severity (TABLE 2). Of note, microbiological diagnosis in CAP cannot be obtained in up to 50% of patients[5]. In patients with CAP who do not need hospital admission, obtaining samples such as sputum and pharyngeal swabs is optional or not recommended in recent guidelines[5]. In patients requiring hospitalization, obtaining good-quality sputum and blood samples, as well as pharyngeal swabs (for PCR), is recommended. Sputum is the most common respiratory sample in patients with CAP, and samples should be collected before antibiotic treatment.

The sensitivity of Gram staining for a sputum sample is ~80% in patients with pneumococcal pneumonia and 78% in patients with pneumonia caused by *Staphylococcus* spp., and the specificity is 93–96%[191,192]. Most health care institutions perform viral PCR on pharyngeal swabs during the influenza season. In the COVID-19 pandemic, it is recommended that all patients admitted with CAP receive a PCR test for the detection of SARS-COV-2.

In patients requiring ICU admission, in addition to all tests mentioned above, bronchoscopic samples, such as bronchoalveolar lavage (BAL) in intubated patients, are not difficult to obtain and provide information on the lower respiratory tract microbiota. Urinary antigen detection tests for *S. pneumoniae* and *L. pneumophila* have good sensitivity and specificity, are not extremely expensive and are recommended in all hospitalized patients.

In patients with HAP or VAP, international guidelines[4] recommend obtaining distal respiratory samples for semiquantitative or quantitative cultures (TABLE 3). In patients with HAP, bronchoscopy is not easy to perform, and sputum samples are not often collected. In patients with VAP, distal respiratory samples are preferred. BAL (performed with or without concomitant bronchoscopy) is the sample that provides most information, as, in addition to cultures, cellularity analysis and PCR can be performed on the fluid. A recent meta-analysis showed that Gram staining of BAL performs well in detecting *S. aureus*[193]. Respiratory samples from patients with HAP or VAP have to be collected before the initiation of a new antibiotic treatment to avoid false-negative cultures. International guidelines[4] do not recommend using procalcitonin (PCT) for the initial diagnosis of HAP or VAP, as several studies have shown that it lacks diagnostic value[194].

Since the 2000s, owing to multiple outbreaks, epidemics and pandemics caused by respiratory viruses in particular, several molecular tests have been developed, which have contributed to widened availability of molecular testing for the aetiological diagnosis of CAP. Molecular tests have several advantages, including detecting low levels of microbial genetic material, remaining unaffected by prior antibiotic therapy, and providing results within a clinically relevant time frame[195]. Molecular tests based on multiplex PCR have been developed to simultaneously detect and quantify multiple respiratory pathogens, as well as some genes related to antimicrobial resistance. Several commercial multiplex platforms are currently available for comprehensive molecular testing for respiratory pathogens that cause pneumonia (respiratory viruses, bacteria and fungi) and for the main resistance genes of the most common bacteria causing pneumonia[195–198].

The WHO currently recommends COVID-19 diagnosis by molecular tests that detect SARS-CoV-2 RNA. SARS-CoV-2 viral sequences can be detected by real-time reverse transcriptase (RT-PCR) in nasopharyngeal swab samples[199]. The disadvantage of this method is that it requires specialized equipment and trained personnel. Additionally, two types of rapid tests are available for COVID-19 diagnosis. The direct SARS-CoV-2 antigen test detects viral components present during infection in samples such as nasopharyngeal secretions, and, therefore, can indicate whether an individual is currently carrying the virus. The indirect antibody test detects antibodies that can be found in serum as part of the immune response against the SARS-CoV-2; thus, it can yield false-negative results if performed before the antibody response has developed and cannot distinguish between past and current infections. These two tests are relatively simple to perform and interpret, requiring limited test operator training[199].

Screening

Some biomarkers may be helpful in identifying which patients are likely to have bacterial pneumonia, in deciding whether antibiotic therapy should be administered, in determining prognosis and in facilitating decisions related to the site of care. However, biomarkers should only be used as an adjunctive tool when managing CAP, as no biomarker has proven full utility in predicting clinical outcomes in patients.

The most widely used biomarkers are acute phase reactants such as C-reactive protein (CRP) and PCT[200]. However, their serum kinetics differ: CRP levels increase after the first 3 days of infection (peak time from infection is 36–50 h), whereas PCT levels rise rapidly (peak time from infection is 12–24 h) in response to microbial toxins or host responses. These properties are useful in differentiating CAP from other non-infectious causes. CRP levels increase in response to any inflammation, and can be modified by the presence of corticosteroids and previous antibiotic therapy, whereas PCT is more specific in bacterial pneumonia. Viral infection-related cytokines attenuate induction of CRP and PCT; however, some elevation in their levels can occur when pneumonia is caused by atypical pathogens (for example, *Mycoplasma* spp., *Chlamydia* spp. and *Legionella* spp.)[201].

Both CRP and PCT can assist in the clinical diagnosis of pneumonia, but CRP and PCT cannot be used in isolation as a basis for treatment decisions. A second test after 24–48 h is mandatory to monitor for any increases. Clinicians should also consider the pattern in the days preceding symptom onset in patients with CAP and whether a patient is taking medication that could have modified these values. For patients with radiographic CAP, PCT levels can be used with clinical assessment to identify those individuals from whom antibiotic therapy

Table 2 | **Microbiological diagnosis of CAP**

Setting	Patient group	Microbiological tests
Outpatient	–	Not routinely performed
Ward[a]	–	Gram stain, sputum culture and urinary antigen test (for pneumococcus and *Legionella*)
ICU[a]	Non-mechanically ventilated patients	Gram stain, sputum culture, blood culture, urinary antigen test (for pneumococcus and *Legionella*) and PCR for respiratory viruses and MRSA in pharyngeal swab
	Mechanically ventilated patients	Culture of endotracheal aspirate and bronchoscopy samples (bronchoalveolar lavage if possible) and PCR for respiratory viruses and MRSA in pharyngeal swab

CAP, community-acquired pneumonia; ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*. [a]Molecular tests for influenza viruses are recommended when influenza viruses are circulating in the community.

Table 3 | **Microbiological diagnosis of HAP and VAP**

Type of pneumonia	Guidelines	Microbiological tests
HAP	–	Gram stain and sputum culture, blood culture, urinary antigens, PCR for MRSA in pharyngeal swab, and culture of bronchoscopy samples if possible
VAP	ATS guidelines[4]	Non-invasive respiratory sampling (via endotracheal aspiration) with semiquantitative cultures, blood culture, PCR for MRSA in pharyngeal swab
	ERS guidelines	Quantitative cultures from distal samples obtained before antibiotic treatment in clinically stable patients

ATS, American Thoracic Society; ERS, European Respiratory Society; HAP, hospital-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilation-associated pneumonia.

can be safely withheld. This assessment can be combined with a PCR test to identify viral infection, especially as new data show that viruses can frequently be a cause of CAP[13,75]. However, caution should be used when a mixed viral–bacterial infection is considered. The new American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) CAP[5] guidelines do not recommend using PCT to determine the need for initial antibacterial therapy. The current recommendation is that empirical antibiotic therapy should be initiated in adults with clinically suspected and radiographically confirmed CAP, regardless of initial PCT level.

In studies in patients with HAP or VAP, in whom biomarkers had been monitored serially since before infection, steady increases or persistent elevations in CRP levels were shown to be associated with a high risk of VAP[202]. However, no such pattern was shown for PCT values (crude values or kinetics), with poor diagnostic accuracy for VAP[203]. Thus, a recent international consensus concluded that a combination of clinical assessment including PCT levels in well-defined antibiotic stewardship algorithms could improve diagnosis of bacterial infections and support antibiotic effectiveness[204].

Prevention of CAP

Many factors increase the risk of CAP and can generally be divided into host factors (for example, age, and the presence of COPD and other chronic pulmonary diseases, diabetes mellitus and chronic heart failure), unhealthy habits (for example, smoking and excessive alcohol consumption) and medications (for example, immunosuppressive drugs, sedating medications such as opioids, and proton pump inhibitors within the first 3 months of administration[205]). Prevention of CAP is crucial, especially in individuals with these risk factors. Available preventive measures include smoking and alcohol use cessation, improvements in dental hygiene, physical exercise, avoiding contact with children with respiratory infections, and pneumococcal and influenza vaccinations[14]. Implementing these measures in primary and specialized care could help reduce the burden of CAP. Presently, pneumococcal and influenza vaccination are the cornerstones of CAP prevention.

The 23-valent pneumococcal polysaccharide vaccine (PPV23) and the 13-valent pneumococcal conjugate vaccine (PCV13) are currently used in adults. Owing to the demonstrated effectiveness of PPV23 in preventing invasive pneumococcal disease (IPD) in people of ≥65 years of age, the use of the vaccine in this population is recommended in many countries[206]. However, PPV23 effectiveness in preventing non-IPD or CAP due to any cause is much less clear. The effectiveness of PPV23 has been reported to range from 25% to 63% in pneumococcal pneumonia[207,208]; the effectiveness of PCV13 in preventing the first episode of CAP, non-bacteraemic and non-invasive CAP, and IPD due to serotypes contained in the vaccine amongst adults of ≥ 65 years of age has been reported to be 45.6%, 45% and 75%, respectively[209]. Efficacy persisted through the mean follow-up period of 4 years[209]. A post-hoc analysis based on data from the CAPITA trial showed that the effectiveness of PCV13 ranged from 43% to 50.0% for pneumococcal CAP, 36% to 49% for non-bacteraemic and non-invasive pneumococcal CAP, and 67% to 75% for pneumococcal IPD[210]. Of note, the most important measure in reducing pneumococcal CAP burden (bacteraemic and non-bacteraemic) in adults is conjugate vaccine programmes in children. Vaccination with pneumococcal conjugate vaccine in children substantially reduces disease in adults owing to the interruption of transmission and herd protection[211,212].

Influenza vaccination can reduce the risk of complications of influenza, such as pneumonia, and is associated with a decrease in severity, hospitalization, ICU admission and mortality associated with influenza[213,214]. All age groups can be affected by influenza virus infection; however, older individuals, young children, pregnant women and those with underlying medical conditions have the highest risk of severe complications. In 2019, a study[75] found that viral sepsis was present in 19% of patients with CAP admitted to ICU and in 61% of patients with viral CAP; influenza virus was the main aetiology. More recently, a study[215] found influenza virus in 23% of patients with LRTI; 57% of these patients had radiographically confirmed CAP. The authors reported 35% vaccine effectiveness against influenza virus LRTI and 51% against influenza-associated CAP. These data demonstrate the importance of an annual influenza vaccination, especially in at-risk groups.

Prevention of HAP

HAP is the leading cause of death from hospital-acquired infection; however, only limited effort has been made in developing prevention strategies. HAP occurs owing to pharyngeal colonization with pathogenic organisms and, in the case of VAP, subsequent aspiration. Thus, oral care and precautions against aspiration may attenuate some of the risk. Although oral and/or digestive decontamination with antibiotics may also be effective, this approach could increase the risk of selecting resistant organisms. Other preventive measures, including isolation practices, remain theoretical or experimental. Indeed, most potential prevention strategies for HAP remain unproven[216].

The individual measures included in prevention bundles can be divided into non-pharmacological and pharmacological categories. To date, most of our knowledge

in HAP prevention is extrapolated from prevention strategies for VAP. An important concept in these strategies is that no single measure is deemed adequate to ensure prevention, with prevention bundles advocated instead. A prospective, interventional, multicentre study in Spain, the Pneumonia Zero project[217], which included 181 ICUs and built on the experience from a previous study[218], suggested VAP prevention via a bundle of mandatory and highly recommended measures. The mandatory measures were education and training of medical staff in airway management, hand hygiene with alcohol solutions, oral hygiene with an antiseptic (chlorhexidine), semirecumbent positioning and promotion of procedures and protocols that safely avoid or reduce duration of mechanical ventilation. The highly recommended measures were aspiration of subglottic secretions (removal of secretions that accumulate above the endotracheal tube cuff, in patients who were expected to be mechanically ventilated for >72 h), selective digestive decontamination (SDD)), and selective oropharyngeal decontamination (SOD) (prophylactic strategies to prevent or minimize infections in critically ill patients, based on the application of non-absorbable antibiotics in the oropharynx and gastrointestinal tract (SDD) or oropharynx (SOD) of patients). When implemented, these measures enabled a decrease in adjusted frequency of VAP from 9.83 to 4.34 per 1,000 ventilator-days over 21 months; similarly, the percentage of patients with VAP significantly decreased from 2.4% to 1.9%. In the ICUs with prolonged participation in the study (19–21 months), the incidence of VAP significantly decreased further to just 1.2%. Finally, significant decreases were observed in VAP recurrence rates (from 10.9% to 7.7%).

Non-pharmacological measures. Good hand hygiene using alcohol solution before airway management is firmly established as a fundamental component of clinical practice. Its inclusion in the VAP care bundle represents an opportunity to audit compliance with, and optimize the quality of, hand hygiene practices[217,219].

Remaining in the supine position[220], the use of gastric tubes and the presence of contents in the stomach contribute to the reflux of gastric contents, aspiration and VAP. Semirecumbent positioning at 30–60° may help to avoid these problems, as found in a 2016 meta-analysis[221]. The lateral Trendelenburg body position (the patient is positioned inclined with head down and feet elevated) has shown no substantial benefit, with research even showing an increase in the number of adverse events[222]. However, based on the results of a post-hoc analysis of the Gravity VAP trial, patients without pulmonary infiltrates at intubation and with no contraindications for the approach may benefit from this position for a short period[222]. The prone position is used to improve hypoxaemia in patients with severe ARDS[223]. This measure is frequently used in COVID-19-associated ARDS[224,225]. This approach might decrease the incidence of VAP, as it facilitates the drainage of secretions compared with a semirecumbent position[226]. Further confirmation is needed to assess the beneficial effect in reducing VAP in patients with COVID-19.

Endotracheal tubes also have an important role in the pathogenesis of VAP, and removing contaminated oropharyngeal secretions can reduce the risk of VAP. In a meta-analysis from 2016, evidence supported the use of endotracheal tubes with subglottic secretion drainage to decrease the rate of VAP[227]. Maintaining cuff pressure at >25 cmH_2O may further prevent the leakage of bacterial pathogens into the lower respiratory tract[217], and continuous cuff pressure regulation could be superior to intermittent control for preventing VAP[228]. Finally, the tube cuff shape and material may have a role in the aspiration of secretions; a randomized, multicentre trial showed that cuffs made of polyurethane or of a conical shape were not superior to conventional cylindrical polyvinyl chloride cuffs in preventing tracheal colonization and VAP[229].

Pharmacological measures. Oral washing with chlorhexidine seems to be effective in preventing VAP; however, a recent meta-analysis[230] showed a trend for increased mortality in patients who received chlorhexidine. Consequently, recent international guidelines[3] did not recommend its use. It is plausible that this increased mortality could be due to direct lung toxicity from aspirated chlorhexidine.

Furthermore, the use of either SOD or SDD remains controversial, with most studies to date being performed in settings with low prevalence rates of MDR or XDR microorganisms. These studies have shown a decrease in both the incidence of VAP and overall mortality[231]. However, in a recent cluster randomized clinical trial performed in units with high rates of MDR or XDR pathogens, SOD and SDD were not effective in decreasing bacteraemia caused by those microorganisms[232]. SDD and SOD are not applied in many centres in the USA and in Europe, primarily for fear of inducing microbial resistance. Owing to the unclear balance between a potential reduction in pneumonia rate and a potential increase in mortality, the 2017 international guidelines[3] decided not to issue a recommendation on the use of chlorhexidine for SOD in patients requiring mechanical ventilation until more safety data becomes available. However, the guidelines did suggest the use of SOD — but not SDD — in settings with low rates of antibiotic-resistant bacteria and low antibiotic consumption. Although establishing a cut-off value for low and high resistance settings is a dilemma, the committee felt that a 5% threshold was reasonable.

Prevention of recurrent pneumonia

Recurrent pneumonia affects ~9% of patients hospitalized with CAP[233,234]. The main factors related to recurrent pneumonia are age ≥65 years, lack of pneumococcal vaccination, previous episode of pneumonia, COPD and corticoid therapy. *S. pneumoniae* is the most frequently identified pathogen in patients with recurrent pneumonia[233,234]. The main preventive measures for recurrent pneumonia are vaccination and adequate control of prior comorbidities, especially in an older population who have an increased risk of infection.

Management

Antibiotics are the mainstay of therapy for pneumonia; however, the agents used depend on a variety of host and pathogen factors. Ideally, therapy should be pathogen-directed, even though a pathogen is often not identified. Nevertheless, as therapy must be started promptly, empirical therapy directed at the most likely aetiological pathogens is required. Because empirical therapy may be more broad-spectrum than definitive therapy, it is often necessary to narrow and target antibiotics once diagnostic testing results become available, usually after 48–72 h. Such a strategy is referred to as a 'de-escalation' of therapy[235]. Rapid comprehensive multiplex molecular methods have been cleared by the FDA and provide results within 2–4.5 h, prior to obtaining final diagnostic testing data. These methods include antibiotic resistance markers and facilitate identification of specific viruses and bacteria, thereby aiding in therapeutic choices and the escalation, de-escalation or cessation of antibiotics.

Considerations for therapeutic choices

Relevant host factors for choosing the type of empirical therapy are severity of illness, the presence of specific medical comorbidities and certain historical data. In detail, these include: chronic lung, heart or liver disease; diabetes mellitus; asplenia; alcohol use disorder; malignancy; malnutrition; recent hospitalization, antibiotic use or colonization by drug-resistant bacteria; the presence of risk factors for aspiration of gastric contents into the lungs (such as impaired swallowing, vomiting, altered consciousness and impaired cough reflex); and recent contact with a health care environment (for example, patients requiring haemodialysis)[236]. It is also important to know epidemiological data regarding individual patients. Seasonal viruses such as influenza viruses are worth examining during the autumn and winter. Contact with someone known to have an illness transmitted by an airborne route (for example, tuberculosis) is also relevant. Similarly, residence in an area with endemic mycoses is a risk for certain fungal pneumonias. Finally, an ICU with a high rate of drug-resistant pathogens poses a risk factor for VAP caused by such organisms[3].

The site of pneumonia acquisition is also an important consideration, namely, in the community, hospital or ICU, or whilst on mechanical ventilation. Since the late 1990s, guidelines have been developed for patients with pneumonia in each of these settings; however, recent data suggest that patient risk factors, and not the site of infection, should be the main determinant for empirical antibiotic choice. Recently, a unified algorithm based on these risk factors has been proposed for all patients with pneumonia[236].

In addition to choosing an antibiotic that is likely to target the aetiological pathogens, it is equally important to determine the right dose and route of administration, to ensure that the drug penetrates into the site of infection. In general, oral therapy is used in patients with less severe illness, whilst intravenous therapy is administered in patients with more serious illness. Aerosolized therapy can be used to boost drug delivery to infected lung tissue, especially if the chosen drugs penetrate into the lung poorly. When treating a critically ill patient with pneumonia and a MDR pathogen, it may be necessary to use high doses to ensure reaching bactericidal drug concentrations at the site of infection. Continuous or prolonged infusion may be needed in the case of β-lactam antibiotics to maximize the time during which the drug concentration exceeds the minimum inhibitory concentration (MIC) of the target organism. Other drugs, such as aminoglycosides, kill bacteria in a concentration-dependent fashion and are best administered at high dosages given once daily[237]. In young patients with pneumonia and sepsis, drug clearance by the kidney may be accelerated (augmented renal clearance), and dosing will need to be increased appropriately[238]. In those with renal impairment, dosing or the frequency of administration may need to be reduced and can be optimized by therapeutic drug monitoring, if available.

CAP therapy

Guidelines for CAP recommend empirical therapy based on the severity of illness and presence of risk factors for specific complex pathogens[5,53,239] (TABLE 4). In the past, patients with risk factors that included contact with a health care environment (haemodialysis, recent hospitalization, residence in a nursing home) were considered to have HCAP and were treated differently from patients with CAP. The new guidelines have eliminated HCAP as a category and recommended that these patients be treated as having CAP. Without forgoing consideration of the local frequency of penicillin and macrolide resistance, every patient with CAP should be treated for pneumococcus in most parts of the world. In addition, atypical pathogens may have a role, often as co-infecting agents; studies showed improved patient outcomes when macrolides or quinolones were added to β-lactam therapy in patients with CAP, particularly those with more severe illness[240], suggesting a need to treat atypical pathogens in many patients with CAP. Patients with more severe illness may need empirical therapy for MRSA and/or *P. aeruginosa*, especially if colonization had occurred previously following influenza (in the case of MRSA) or after prior use of broad-spectrum antibiotics (for both pathogens)[241].

Although in many patients CAP may have a viral aetiology, either as a single pathogen or as part of a mixed infection, antiviral therapy is not routinely recommended. However, for documented influenza-associated pneumonia, current guidelines recommend the use of an anti-influenza agent such as oseltamivir, regardless of illness duration[5]. Nonetheless, the benefit of these agents is greatest within the first 48 h of infection onset. Thus, in patients with a high suspicion of influenza, therapy should be started, whilst results from diagnostic testing are pending. Additionally, even with documented influenza, antibiotics should be used empirically to account for possible bacterial superinfection[5].

Outpatients. For outpatients without comorbidities or risk factors for MDR pathogen infection, current guidelines recommend monotherapy with respiratory fluroquinolone or combination with amoxicillin–clavulanate or a cephalosporin and macrolide or doxycycline[5].

Table 4 | **Guidelines for initial empirical treatments of hospitalized patients with CAP**

Patient group	Non-severe CAP	Severe CAP[a]	Notes
No special considerations	Standard regimen: a β-lactam and a macrolide; or a respiratory fluroquinolone alone	Standard regimen: a β-lactam and a macrolide; or a β-lactam and a respiratory fluoroquinolone	If clinically suspected or proven *Legionella* spp. infection, a fluoroquinolone is preferred to a macrolide; data show reduced mortality in severe CAP with the addition of a macrolide to a β-lactam
Previous respiratory isolation of MRSA	Standard regimen based on severity and MRSA coverage; it is recommended that cultures be obtained[b] or PCR analysis of a nasal sample performed to either enable de-escalation of therapy or confirm the need for continued therapy		Whilst treating for MRSA, some organisms may produce exotoxins such as the Panton–Valentine leucocidin; thus, therapy may require an additional antibiotic (for example clindamycin or linezolidalone) to suppress toxin generation[304]
Previous respiratory isolation of *P. aeruginosa*	Standard regimen based on severity and coverage for *P. aeruginosa*; it is recommended that cultures be obtained to either enable de-escalation of therapy or confirm the need for continued therapy		–
Recent hospitalization, parenteral antibiotic and locally validated risk factor for MRSA infection	Standard regimen based on severity; obtain cultures but withhold MRSA coverage unless culture results are positive; if rapid PCR analysis of a nasal sample is available, withhold additional empirical therapy against MRSA unless rapid testing is positive and obtain respiratory cultures	Standard regimen and MRSA coverage; and perform PCR analysis of a nasal sample and cultures to either enable de-escalation of therapy or confirm the need for continued therapy	No empirical therapy of MRSA in patients with appropriate risk factors, unless with severe illness; otherwise wait for culture or nasal PCR results; most hospitals do not have locally validated risk factors
Recent hospitalization, parenteral antibiotic and locally validated risk factor for *P. aeruginosa* infection	Standard regimen based on severity; coverage for *P. aeruginosa* only if culture results are positive	Standard regimen and coverage for *P. aeruginosa;* obtain cultures to either enable de-escalation of therapy or confirm the need for continued therapy	No empirical therapy of *P. aeruginosa* in patients with appropriate risk factors, unless with severe illness; otherwise wait for culture results; most hospitals do not have locally validated risk factors

CAP, community-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*. [a]Severe CAP is based on major and minor criteria as per the 2007 American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) guidelines[239]). [b]Culture cannot distinguish colonization from infection. Adapted from the 2019 ATS/IDSA guidelines[5].

Regardless of the prevalence of resistance, good experience with macrolide monotherapy has been reported, suggesting that in vitro resistance is not always clinically relevant unless it is high-level resistance (resulting from a ribosomal mechanism) and not lower-level resistance (caused by efflux pumps)[242]. For example, in a Canadian study, patients with CAP who received macrolide therapy (usually as monotherapy) had lower mortality and hospitalization rates than those receiving alternative therapies[243]. For outpatients with comorbid illnesses, current guidelines recommend therapy with a β-lactam and macrolide combination or monotherapy with a respiratory fluoroquinolone, even though recent concerns about fluoroquinolone toxicity have limited their use[5].

Hospitalized patients. In patients with CAP in hospital wards, therapy should be a β-lactam–macrolide combination or a quinolone (levofloxacin or moxifloxacin) alone (TABLE 4). In areas with a high prevalence of endemic tuberculosis, caution should be exercised with the use of a quinolone, as it can mask the presence of tuberculosis and select for drug-resistant tuberculosis. β-Lactams include ceftriaxone, ceftaroline and ampicillin–sulbactam, whilst macrolides should comprise azithromycin or clarithromycin; some recent data have shown more frequent cardiac complications with the use of erythromycin[244]. Many studies have shown that the addition of a macrolide to the β-lactam, particularly in those with moderately severe illness or with *Legionella* spp. infection, is associated with a lower mortality rate than β-lactam monotherapy[245].

All ICU-admitted patients should receive a combination therapy of a β-lactam and either a macrolide or a quinolone. Admission to ICU should be guided by the presence of one of two major criteria (need for mechanical ventilation or septic shock requiring vasopressors) or three of nine minor criteria, as per the 2007 ATS/IDSA guidelines[239]. In this population, a macrolide is generally preferred, although some studies have shown that a quinolone may prove more effective if *Legionella* spp. infection is highly suspected or documented[246]. If the patient has risk factors for *P. aeruginosa* or MRSA infection, then treatment for such pathogens should be added.

HAP therapy

Patients can develop HAP in or outside the ICU and can be managed with or without mechanical ventilation, although as many as 30% of patients with HAP who are not initially ventilated will require mechanical ventilation[247]. In patients with a predicted mortality risk of <15% based on the presence or absence of septic shock, monotherapy is associated with lower mortality than combination therapy. In patients with a predicted mortality risk of >25%, combination therapy is associated with reduced mortality; the type of therapy has no effect on mortality in those with a predicted mortality risk of 15–25%[248]. MDR pathogen infection should be considered in patients with a history of prior antibiotic therapy or prolonged hospitalization in the previous 3 months, as well as patients hospitalized in an ICU with a >25% rate of MDR pathogen infections. Although empirical therapy can be guided by patient features, each ICU

has its own unique bacteriology; thus, therapy should be guided by knowledge of the local antibiogram[3,249].

Patients with a low mortality risk (estimated from published data in relation to the presence of sepsis and shock) and no MDR pathogen risk factors should receive monotherapy (TABLE 5). In patients with a mortality risk of >15% and/or risk factors for MDR pathogens but who are not in septic shock, monotherapy can be adequate (provided that the chosen antibiotic can target >90% of the gram-negative pathogens in the ICU). Although there is controversy in many hospitals about the need for combination therapy, two agents are often necessary to provide a >90% likelihood of appropriate therapy, especially in the high-risk population and in those with septic shock. The combination regimen should target *P. aeruginosa* and ESBL-producing Enterobacterales. In all patients with HAP, anti-MRSA therapy should be considered and, if necessary, administered with either vancomycin or linezolid. Depending on local epidemiology, some patients will be at risk of infection with *Acinetobacter baumanii*, carbapenem-producing Enterobacterales or *Stenotrophomonas maltophilia*, each one requiring a unique therapy approach. For VAP due to MDR pathogens, such as *Acinetobacter baumanii*, adjunctive inhaled antibiotics (amikacin or colistin) have been added to systemic therapy, with no proven mortality benefit; efficacy may vary with the type of aerosol delivery system used[250].

The duration of HAP therapy is between 7 and 14 days, although most patients are successfully treated within only 7 days[251]. Although not all experts agree, the European guidelines list the following groups as exceptions to short duration therapy: patients with MDR pathogen infection, such as *P. aeruginosa* and *Acinetobacter* spp.; those who received inappropriate therapy initially; those who are severely immunocompromised; and those receiving second-line antibiotic agents[217,252,253]. Current guidelines do not strongly endorse biomarkers such as PCT to guide therapy duration for HAP and VAP, although some randomized trial data do show efficacy for this approach[254].

Therapy in immunocompromised patients

Immunocompromised patients can develop pneumonia due to the common community and nosocomial pathogens present in the setting as well as other pathogens related to a specific type of immune dysfunction and/or resistant bacteria, viruses, fungi and parasites. Common conditions that impair the immune system include malignancy, HIV infection with a $CD4^+$ T cell count of <200 cells per mm^3, and solid organ or stem cell transplantation. Therapies that cause immune suppression include prednisone, biological disease modifiers, and chemotherapeutic agents such as azathioprine, methotrexate and cyclophosphamide.

Although empirical therapy is often used, the range of possible pathogens in this population is so broad that aggressive diagnostic testing is necessary, including sampling of deep lower respiratory tract secretions with bronchoscopy in most patients[255]. In patients with HIV infection and a low $CD4^+$ T cell count or with recent corticosteroid tapering, therapy should target common pathogens and *Pneumocystis jirovecii*[256]. Patients with severe neutropenia, steroid-induced immune suppression and those receiving biologic response modifiers (such as tumour necrosis factor inhibitors) can be infected with fungi such as *Aspergillus* spp. or Mucorales. Diagnostic testing in those with malignancy or drug-induced immune suppression should also consider other opportunistic pathogens, including cytomegalovirus, Varicella zoster virus, *Nocardia* spp., parasites such as *Strongyloides stercoralis* and *Toxoplasma gondii*, and *Mycobacterium tuberculosis* (for example, owing to a re-emergence of latent infection).

Aspiration pneumonia therapy

Patients with witnessed macro-aspiration of gastric or oral contents into the lung can develop chemical or bacterial pneumonitis, or simply have bland aspiration. If bacterial pneumonia occurs, patients should receive antibiotics aimed at common community or nosocomial pathogens that were likely to be colonizing the oral and gastric tract at the time of aspiration. In community aspiration, therapy is the same as in CAP unless the patient has poor dentition, which can make infection by anaerobic pathogens possible owing to favourable growth conditions for such microbes in the patient's mouth. When patients with poor dentition have a lung infiltrate after a witnessed or clinically suspected aspiration event, therapy should be a β-lactam such as ampicillin–sulbactam or amoxicillin–clavulanate, or a quinolone, such as levofloxacin or moxifloxacin. Any of these drugs could also be

Table 5 | **Proposed initial empiric treatments of patients with HAP**

Patient group		Therapy	Notes
Low mortality risk, no MDR pathogen risk factors		Monotherapy (ceftriaxone, cefotaxime, ertapenem, levofloxacin or moxifloxacin); consider MRSA therapy	Data show efficacy of these agents, provided that their efficacy is supported by local microbiological data
High mortality risk and/or MDR pathogen risk factors	No septic shock	Monotherapy (ceftriaxone, cefotaxime, ertapenem, levofloxacin or moxifloxacin); consider MRSA therapy	Data show efficacy of these agents, provided that their efficacy is supported by local microbiological data; therapy could comprise the anti-pseudomonal β-lactam cefepime, imipenem, meropenem or piperacillin–tazobactam, if *P. aeruginosa* is a concern[3]
	With septic shock	Combination therapy; consider MRSA therapy	An anti-pseudomonal β-lactam plus either an aminoglycoside or quinolone (ciprofloxacin or levofloxacin)

HAP, hospital-acquired pneumonia; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*.

used if dentition is normal; alternatively, ceftriaxone would be effective[1]. For those with nosocomial aspiration, therapy should be based on the presence of risk factors for MDR pathogens and aimed at common, local and drug-resistant organisms, similar to therapy in other forms of nosocomial pneumonia. There is no need to add specific anti-anaerobic coverage, as these organisms are uncommon in patients who aspirate whilst in hospital or chronic care facilities[257].

Adjunctive therapy

In addition to antibiotics, patients with severe illness might benefit from adjunctive corticosteroid therapy. In general, this therapy should be restricted to those with severe CAP and a high inflammatory response[258]. In one trial, methylprednisolone was more effective than placebo, leading to less treatment failure (especially late failure) in a population with both severe CAP and elevated CRP levels in the serum[259]. However, before using corticosteroids, it is necessary to rule out influenza, as it may worsen with this line of therapy[260]. By contrast, studies in patients with COVID-19 and hypoxaemic respiratory failure have shown a benefit of corticosteroid therapy with dexamethasone[261]. Similarly, IgM-enriched immunoglobulin may be useful in patients with severe CAP, and high CRP levels and low IgM levels in the serum. In a randomized, double-blind, placebo-controlled trial, IgM-enriched immunoglobulin led to a reduction in mortality and an increase in ventilator-free days in this population, when compared with placebo[262].

Another adjunctive and supportive therapy includes management of hypoxaemia with respiratory failure, which may necessitate mechanical ventilator support. However, some studies show that patients with CAP can be managed with either non-invasive ventilation or high-flow oxygen. Either modality can reduce the need for mechanical ventilation and, therefore, avoid some of the complications associated with endotracheal intubation and ventilation[263].

Follow-up of patients after pneumonia

In some patients with CAP, pneumonia can be the start of an inexorable downhill course. In one study, the long-term mortality of patients of >65 years of age hospitalized with CAP far exceeded the in-hospital mortality (33.6% and 11%, respectively)[264]. In some studies, this long-term effect has been attributed to cardiac events that were initiated by acute lung infection[155].

Pneumonia recurrence can occur in all forms of pneumonia. Recurrence should be classified on the basis of the site of infection. If re-infection occurs at the same site as the original infection, consideration should be given to local factors such as endobronchial obstruction (due to a tumour or foreign body), focal bronchiectasis, insufficient duration of therapy, or infection with a drug-resistant or inadequately treated pathogen. Recurrence elsewhere could be due to immune impairment (due to comorbid illness or certain medications), a non-infectious pulmonary process or recurrent aspiration.

Routine follow-up chest radiography after CAP is not generally recommended. However, if it is prescribed (to monitor resolution of a pleural effusion or infiltrate suggestive of a possible lung mass), it should be delayed for 4–6 weeks if the patient is responding well to therapy[5]. During follow-up, patients should be monitored for undiagnosed or ineffectively managed comorbid illness and encouraged to avoid cigarette smoking. Patients should also have up-to-date pneumococcal and influenza vaccinations. The 30-day readmission rate for patients with CAP has been found to vary from 16.8% to 20.1%[167]. Pneumonia itself was the cause of readmission in only 17.9–29.4% of patients; however, other common causes were exacerbations of congestive heart failure or COPD[167]. Patients with health-care-associated risk factors have a higher probability of readmission than patients with uncomplicated CAP[265].

Quality of life

The effect of pneumonia is heavily influenced by both the origin of the disease (within the community or in health care environments) and its severity[266]. Most data regarding the effect on quality of life have been obtained in patients with CAP[171]. Antibiotic treatment starts to improve pneumonia symptoms rapidly; acute symptoms typically improve within 3–5 days in patients with mild CAP (outpatients) and 5–10 days in hospitalized patients with more severe CAP not requiring ICU admission; however, return to baseline levels of symptoms and function seems to take substantially longer[172,267–269]. In mild-to-moderate CAP, in most patients symptoms such as cough and breathlessness resolve within 14 days, although up to 6 months are required for full recovery[267]. Thus, the greatest burden seems to be a loss of function in the long term. Delayed recovery is associated with the number of comorbid conditions. In most cases, the presence of ongoing health impairment is largely related to a decompensation of underlying diseases rather than the ongoing acute symptoms of CAP[267]. A modelling study showed that in hospitalized patients with CAP, these acute symptoms reduced in intensity by ~50% within the first 3–5 days, and resolved in nearly all patients by day 28 (REF.[268]). There does not seem to be a meaningful difference in symptom intensity or time to symptom resolution between viral and bacterial pneumonia[270].

A French study in patients with pneumococcal pneumonia followed for 12 months after hospital discharge used the EQ-5D-3L questionnaire to evaluate health status[271]. Patients experienced a progressive improvement in quality of life after discharge, plateauing at six months. Importantly, quality of life either did not improve or deteriorated after discharge in 34% of patients; recovery was worse in old patients than in young patients. In a US study in patients with CAP, on average, patients were able to return to normal productivity in 3 weeks and missed 2 weeks of work[272]. Recovery was slowest in patients with comorbidities such as COPD, leading to recovery times of 2 months on average. Even after recovery, symptom scores in patients with CAP are worse than those in the general population, partially because CAP has a long-term effect on health. Another partial reason for these lower scores is the development of CAP in patients with high-risk comorbidities, which make these patients more symptomatic than the general population[273]. Lastly, long-term mortality is increased in patients with CAP compared

with the general population[35]. LRTIs without radiographic infiltrates (non-CAP LRTIs) are associated with a similar impairment in quality of life to CAP[274].

Studies comparing quality of life between patients with CAP and the general population have shown consistently worse quality of life up to 12 months after CAP. With a few exceptions, most of these studies used generic quality of life and productivity tools. A systematic review identified five CAP-specific, patient-reported outcome measures, of which the CAP symptom questionnaire (CAP-sym) was the most widely used[275]. This review concluded that most CAP-specific tools have thus far been evaluated in highly specific populations and may not be fully representative, and it recommends continuing to use generic tools until better tools are available.

Outlook

Improved diagnostics

The key to a switch to pathogen-specific therapy is an accurate aetiological diagnosis, and the availability of rapid molecular diagnostic tests makes clinical trials and subsequent clinical use of these targeted therapies feasible. Most progress in diagnostics can be observed in two areas: rapid identification of pathogens in positive blood cultures and detection of respiratory viral pathogens. However, bacteraemia is uncommon in pneumonia and, therefore, the effect of these molecular assays on management is limited. By contrast, PCR diagnosis of respiratory viral infections has now become the standard of care. The greatest issue with these assays obtained from nasopharyngeal specimens is whether results reflect upper respiratory tract infections only or accurately detect the cause of pneumonia. In addition, negative nasopharyngeal samples have occurred in patients with positive concurrent bronchoalveolar samples for influenza and SARS-CoV-2 (REF.[276]).

Several multiplex PCR platforms are available for clinical use for bacterial pneumonia, with approval based on comparison with standard diagnostic tools, specifically culture[277,278]. However, as culture itself is not a gold standard, the true operating characteristics of the tests remain unknown. One alternative is metagenomics sequencing to determine all microbiota present; clinically relevant platforms are available[279,280]. Generally, these molecular assays are more sensitive than culture, especially for fastidious microorganisms; nevertheless, none of the current multiplex assays detect all of the relevant pathogens and, therefore, cannot replace cultures. In addition, a limited ability to provide information on antibiotic susceptibility is a major weakness. Despite such limitations, substantial impact on antibiotic prescription is possible. Most evaluations to date comprise observational studies and analyses of the theoretical benefit if antibiotic decisions based on molecular assays were applied prospectively. Perhaps the best demonstration of such potential is to limit the use of vancomycin or linezolid for suspected MRSA pneumonia[197]. Multiple sensitive and specific gene targets for *S. aureus* identification are available, whilst the absence of the *mecA* gene detection essentially excludes methicillin resistance in that isolate; thus, a negative assay eliminates the need for MRSA coverage. However, the greatest hurdle for molecular assays is clinicians' willingness to base antimicrobial treatment on results obtained from these novel diagnostic platforms; even a BAL assay with a 98% negative predictive value did not result in a decrease in empirical treatment of VAP[281]. Implementation trials are required to demonstrate the true benefit of more accurate diagnostics.

Improved diagnostic testing may enable a host of unanswered epidemiological matters surrounding pneumonia to be addressed. A leading question in the field of pneumonia is its cause in immunocompromised patients; only expert opinion guides treatment recommendations[256]. The COVID-19 pandemic also illustrates the probable high frequency of additional viral agents that may cause CAP of seemingly unknown aetiology[13]. The role of fungal superinfection of viral pneumonia also remains controversial owing to diagnostic uncertainty[282].

Antibiotic therapy

For most of the ~75-year history of antibiotic treatment of pneumonia, the backbone of therapy has been a β-lactam[283]. The emergence of bacterial resistance to β-lactams has been tackled with two strategies: newer generations or types of β-lactams (penicillins, cephalosporins and carbapenems)[284–288] and combinations with β-lactamase inhibitors (BLIs). Ceftolozane is the newest β-lactam on the market; it has improved activity against *P. aeruginosa* compared with other cephalosporins[284]. Each BLI has slightly different activity against the variety of resistance mechanisms in Enterobacterales, including carbapenem-resistant and ESBL-producing Enterobacterales, which may affect local efficacy owing to geographical differences in resistance patterns[289].

Each new drug had been intended to replace the prior generation, gain a large proportion of market share and, therefore, justify the large development costs for the pharmaceutical industry. However, the majority of infections, especially community-acquired[13], remain susceptible to cheap generic antibiotics even today, and the probability of a new blockbuster drug that would garner a large market share is progressively in decline[290]. This and multiple other factors, including increased costs for registration trials, a regulatory environment and challenges in clinical trial design, have led many pharmaceutical firms to abandon antibiotic development, as it offers a poor return on investment[291].

Nevertheless, the paradigm for antibiotic development has shifted and, since the 2000s, niche antibiotics, particularly for gram-negative pathogens, have progressively emerged, developed by small biotech companies. These niche antibiotics specifically address gaps in standard antibiotic treatment coverage, yet leverage high prices to compensate for a small market share. The future success of these niche antibiotics could be increased by the emergence of rapid diagnostic tests that can detect specific pathogens or specific resistance markers immediately.

New antibiotics. The first generation of niche antibiotics were new β-lactams or BLIs developed for individual MDR or XDR pathogens[292]. The greatest unmet need for pneumonia due to gram-negative pathogens

is for treatment of carbapenem-resistant *Acinetobacter* spp.; the only agent in development specifically for *Acinetobacter* spp. is a combination of two BLIs[293]. Both BLIs also have intrinsic β-lactam activity but are being studied in combination with a carbapenem for serious *Acinetobacter* spp. infections, including pneumonia.

Agents specific for *Pseudomonas* spp. are also in development. Murepavadin is the first of a new class of antibiotics that inhibit the outer membrane assembly of *P. aeruginosa*; other drugs targeting outer membrane assembly are in development, including phage-derived endolysins[294]. Small molecule inhibitors of the type-III secretion apparatus in *P. aeruginosa*, a crucial component of its pathogenesis, are also in development.

One exception to the niche drug approach is cefiderocol, an extremely broad-spectrum agent with activity against almost all MDR pathogens. Cefiderocol links ceftazidime and cefepime together, maintaining the β-lactam bactericidal mechanism whilst enhancing bacterial uptake[295]. Bacteria take up cefiderocol through iron channels, and this mechanism is extremely appealing, as many MDR gram-negative pathogens, including *P. aeruginosa*, *Acinetobacter* spp. and *Stenotrophomonas* spp., avidly take up iron, and a major component of the acute-phase host response is to sequester iron from pathogens. Cefiderocol was non-inferior to high-dose extended-infusion meropenem for HAP due to gram-negative pathogens[296], but it was associated with a higher mortality than the best available therapy for pneumonia and bacteraemia, specifically due to carbapenem-resistant *Acinetobacter* spp.[292].

Lefamulin is the first truly new antibiotic class since the oxazolidinone linezolid. The mechanism of action of lefamulin is via protein synthesis inhibition, and lefamulin is approved for the treatment of CAP based on equivalence to moxifloxacin[297,298]. This drug can be used as a single agent to target MRSA and other CAP pathogens resistant to macrolide, β-lactam and fluoroquinolone antibiotics, and possibly in cases of treatment failure and/or in patients with multiple drug allergies. Unfortunately, lefamulin does not have substantial activity against ESBL-producing gram-negative pathogens, which is an unmet need in CAP.

Non-antibiotic therapy

Monoclonal or polyclonal antibodies to specific MDR pathogens, including *S. aureus* and *P. aeruginosa*, are the ultimate narrow-spectrum agents, being both extremely safe and having the great advantage of not disturbing the commensal microbiota[299,300]. Antibodies against the *P. aeruginosa* type-III secretion apparatus, alginate and other unique targets have entered clinical trials. Several anti-*S. aureus* antibodies have also been developed[301]. The challenge for specific antibodies is whether they should be used for prevention or as adjuncts to antibiotic therapy. The lack of sensitive risk factors or predictive markers for pneumonia caused by a specific pathogen make prophylactic trials difficult and potential clinical use expensive; thus, development for preventive indications has been abandoned for several agents, and attention has shifted to adjunctive use, despite this being associated with loss of the microbiota-sparing effect with this strategy.

Case reports have been published on bacteriophage therapy as an alternative to antibiotics in patients with extremely difficult-to-treat pneumonia[302]. However, major logistic issues must be overcome before phage therapy becomes a legitimate option[303]: the individual patient's isolate must be tested for susceptibility against a battery of bacteria-specific phages; a cocktail of at least three phages is usually needed, owing to the emergence of resistance to any single phage; and the availability of phages and susceptibility testing facilities remain extremely limited. Furthermore, the optimal delivery method, namely aerosolization, instillation or venous infusion, remains unclear. No large-scale clinical trials have been completed.

Lastly, the COVID-19 pandemic has generated a large number of studies of adjuvant treatments focusing on host response to SARS-CoV-2. It remains unclear whether any adjuvant treatments other than corticosteroids that may provide benefit in SARS-CoV-2 infection can be used for influenza or other serious viral pneumonias. However, the COVID-19 pandemic has clearly increased interest in both host-directed therapy and newer antivirals.

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