

# Community-acquired pneumonia: risk factors, prognosis, microbial etiology, treatment, and prophylaxis

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## ABSTRACT

Community-acquired pneumonia (CAP) is a significant global health problem with a considerable clinical burden. It especially affects children under 5 years old, the elderly, people with multiple comorbidities, and the immunocompromised. Despite advances in the diagnosis and treatment of CAP, mortality rates remain high, particularly among patients who develop severe pneumonia with life-threatening complications. Notably, the long-term consequences of CAP include the worsening of pre-existing comorbidities, the development of new medical conditions, and a reduction in life expectancy, especially in older adults. Key factors that influence mortality include the initial severity of disease, the presence of prior comorbidities, and the status of the immune system. This review discusses current scientific evidence and emerging data on various aspects of CAP, including changes in its epidemiology, the role of viral causes, updated treatment approaches, the use of corticosteroids, and available preventive measures.

**Keywords:** Community-acquired pneumonia. Pneumonia. Risk factors. Lung infection.

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## INTRODUCTION

Community-acquired pneumonia (CAP) is a common and fatal infection. It is responsible for 2.1 million deaths annually worldwide according to the 2021 Global Burden of Disease report, especially affecting vulnerable groups, such children under 5 years old, the elderly, individuals with multiple comorbidities, and the immunocompromised (Figure 1)<sup>1</sup>. Over time, however, the epidemiology of pneumonia has changed due to demographic changes in the population, including increased numbers of older and immunocompromised people, advances in diagnostic tests, new therapies, effective vaccination and preventive measures, and the emergence of new pathogens<sup>2,3</sup>.

Poor outcomes are linked to the severity of the infection, patient characteristics and comorbidities, and the pathogen's virulence and resistance characteristics<sup>2</sup>. Evidence indicates that pneumonia should be considered a multisystem disease with the potential for both acute and chronic sequelae. This is especially true in patients developing severe pneumonia that requires intensive care unit (ICU) admission, which represents approximately 10% of all cases hospitalized with CAP<sup>4,5</sup>.

Although CAP is mainly caused by bacteria, the implementation of molecular diagnostic tests suggests that respiratory viruses such as influenza, respiratory syncytial virus (RSV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also frequently cause CAP<sup>2</sup>. Antibiotic resistance and the increasing prevalence of multidrug-resistant organisms also affect the etiology and treatment of

CAP<sup>6</sup>. Continued surveillance, research, and updates to clinical guidelines are crucial to optimizing the management of CAP.

## EPIDEMIOLOGY OF CAP

Globally, CAP remains a common infectious disease with an incidence of 1.2-1.4 cases/1000 people each year<sup>2</sup>. The epidemiology of CAP varies by geographic region and is influenced by age, demographics, socioeconomic factors, changes in pathogens, and the implementation of vaccination schedules. In the United States, data from a recent epidemiological study on CAP<sup>7</sup> reported an incidence of 6.49 cases/1000 people annually, a rate that would correspond to a figure of 1.5 million adults requiring hospitalization. The annual incidence of pneumonia by age, per 1000 people/year, was reported to be 3.27, 20.9, and 39.48 for ages 18-64 years, ≥ 65 years, and ≥ 85 years, respectively, highlighting the greater impact of pneumonia in the elderly<sup>7</sup>. In Europe, the annual incidence of CAP is estimated to at 2-8 cases/1000 people/year overall<sup>8</sup>, increasing to 14-16 cases/1,000 people/year age ≥ 65 years<sup>8</sup>. The difference in CAP incidence between the United States and Europe can be attributed to higher vaccination coverage (pneumococcal and influenza vaccine) in the United States compared with Europe<sup>9,10</sup>. Smoking rates may also be a factor: in the United States, rates decreased from 43% in 1965 to 11.6% in 2022<sup>11</sup>, whereas a recent report in Europe showed that 26% of the European population still smoke<sup>12</sup>.

In Latin America, little information exists about the incidence of pneumonia in adults. Data from one prospective population-based

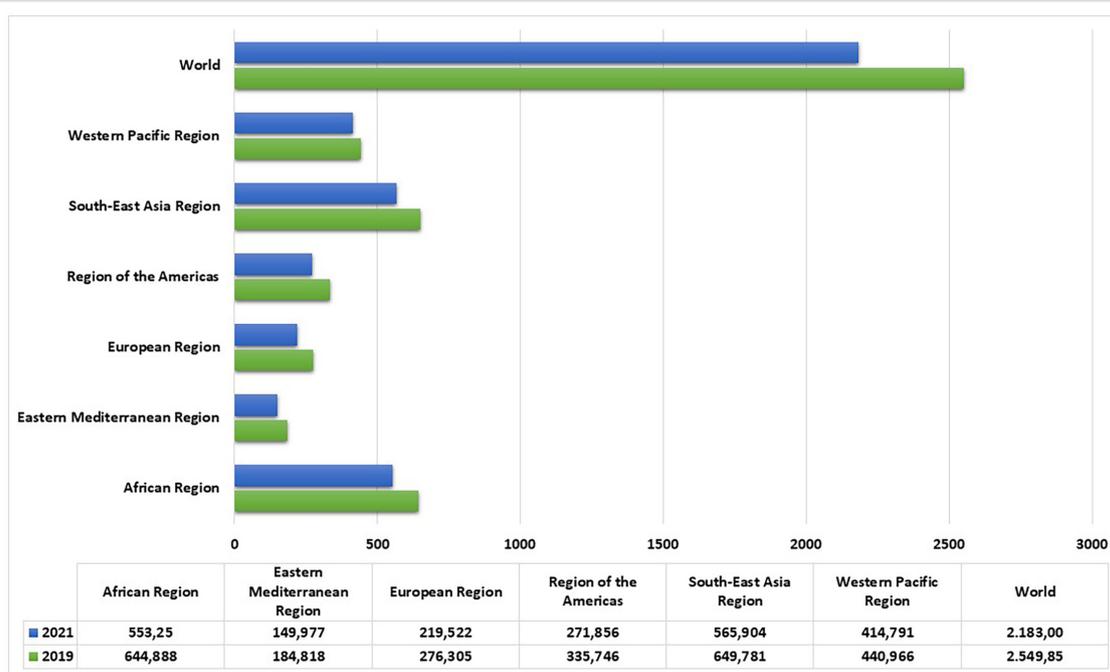


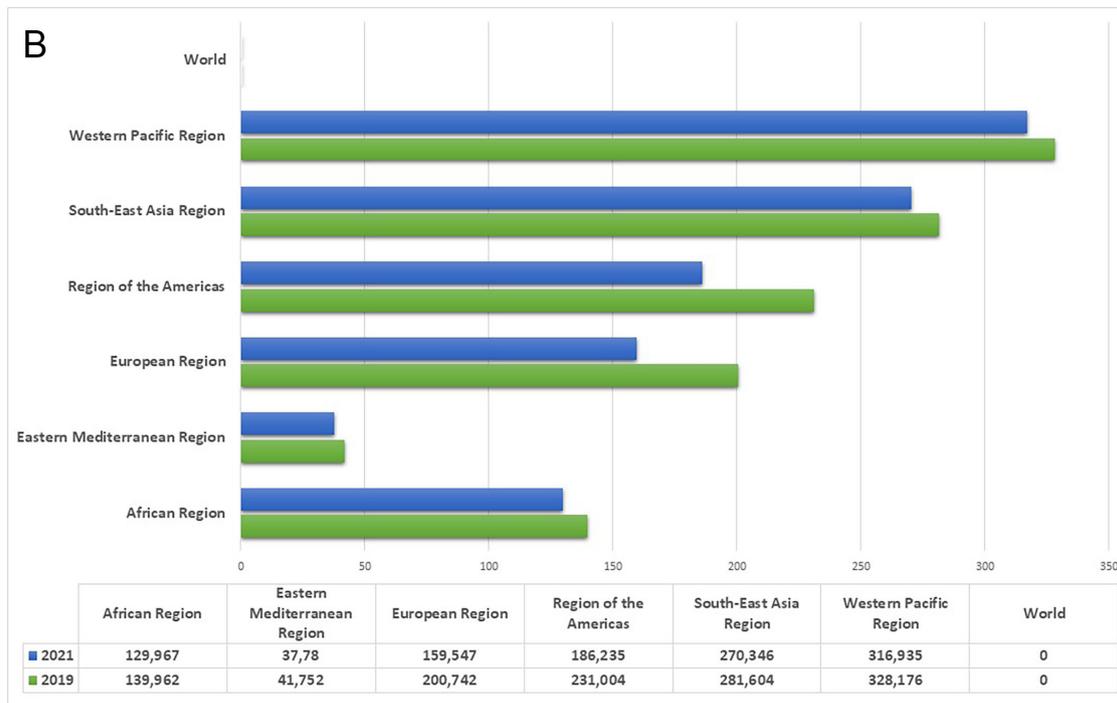
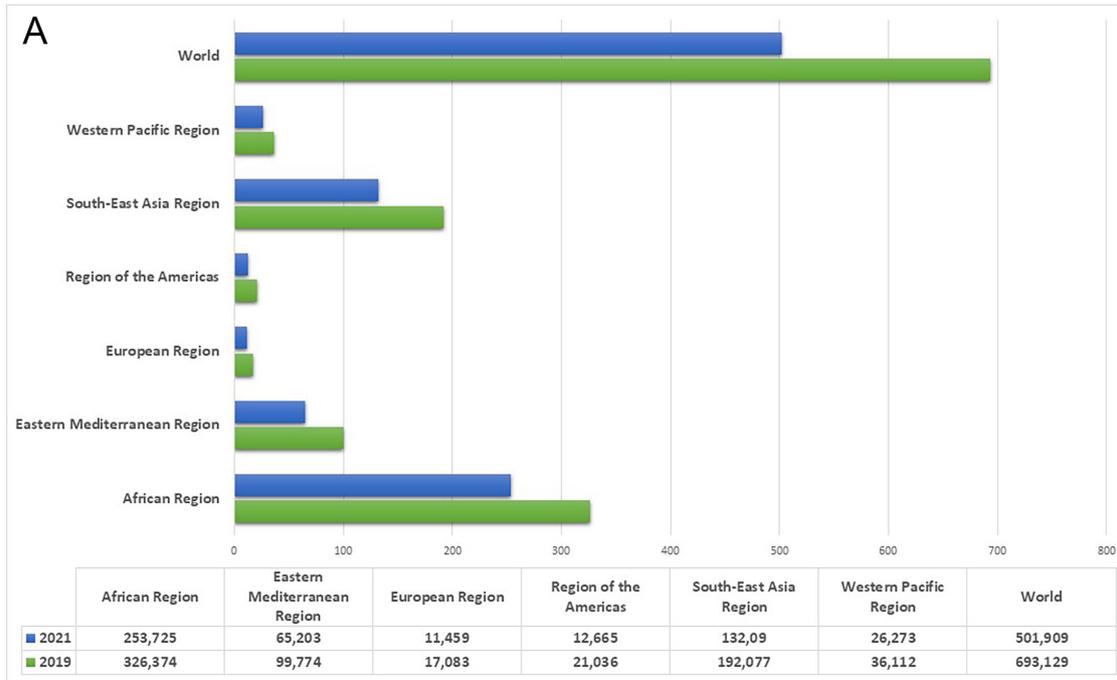
FIGURE 1. Global pneumonia deaths according to the 2021 Global Burden of Disease report.

surveillance study reported that the incidence in three South American cities (General Roca, Argentina; Rivera, Uruguay and Concepción, Paraguay) ranged from 1.76 to 7.03/1000 person-years<sup>13</sup>.

Pneumonia in Africa is associated with a higher burden. There, it particularly affects children younger than 5 years old and the elderly, as well as people with the human immunodeficiency virus (HIV), which affects 25.6 million people in the region<sup>14</sup>. According to 2021 geodatabase data, pneumonia caused 603,000 deaths in Africa, with the highest number of deaths among children younger than 5 years old (271,300 deaths) and people ages 70 years and older (143,200 deaths) (Figs. 2A and 2B)<sup>1</sup>. The HIV epidemic, the higher burden of tuberculosis, and the low coverage of vaccines

increase the risk of pneumonia, hospitalization, and death, especially in younger populations<sup>15</sup>.

The increased number of immunocompromised individuals over the past two decades has had an important impact on the epidemiology of pneumonia<sup>4</sup>. Although this increase is multifactorial, the three main factors are the rise in cancer survival rates, increase in organ transplant recipients, and the increased use of immunosuppressive drugs. In the United States, for example, a study in 2013 reported that immunocompromised individuals accounted for 3% of the adult population<sup>16</sup>, while a more recent study in 2021 found that this figure has risen to 6.6%<sup>17</sup>. The main issue related to the epidemiology of immunocompromised patients is the lack of a standardized definition, which creates a



**FIGURE 2. A:** global pneumonia deaths of children under 5 years old according to the 2021 Global Burden of Disease report. **B:** global pneumonia deaths of adults aged 70 years and over according to the 2021 Global Burden of Disease report.

significant knowledge gap<sup>18</sup>. Two studies have focused on CAP in immunocompromised patients. The first, conducted in the United States, reported that 1 in 10 adults hospitalized with CAP were immunocompromised<sup>19</sup>, while the second, conducted in Europe, reported that two in ten patients were immunocompromised<sup>20</sup>. The true impact of immunocompromise on the epidemiology of pneumonia has yet to be determined.

## RISK FACTORS FOR CAP

Diverse risk factors for pneumonia have been reported in the adult population. Specific populations, such as older adults (ages  $\geq 65$  years)<sup>21,22</sup> with multiples comorbidities<sup>8,23</sup>, are at increased risk of CAP. A systemic review and meta-analysis of 29 observational studies identified the following host-related risk factors for pneumonia: age (adjusted odds ratio [aOR], 1.07; 95% confidence interval [CI], 1.01–1.19 per year of increase), smoking (aOR, 1.57; 95% CI, 1.12–2.77), poor nutritional status (aOR, 6.14; 95% CI, 0.65–11.58), poor oral health (aOR, 6.14; 95% CI, 0.65–11.58), previous pneumonia (aOR, 1.86; 95% CI, 1.53–3.81), use of immunosuppressed drugs (aOR, 3.1; 95% CI, 1.27–15.13), use of oral steroids (aOR, 1.87; 95% CI, 1.30–4.05), and use of proton pump inhibitors or H<sub>2</sub> antagonists (aOR, 1.51; 95% CI, 1.18–1.60)<sup>22</sup>. The comorbidities most frequently associated with an increased risk of pneumonia include chronic respiratory disease, such as chronic obstructive pulmonary disease (COPD) (aOR, 1.99; 95% CI, 0.67–13.53) or asthma (aOR, 1.71; 95% CI, 1.00–4.20)<sup>22</sup>, chronic cardiovascular disease (aOR, 1.4–3.2), cerebrovascular disease (aOR, 1.08–1.68), dementia (aOR, 2.64–2.68), diabetes mellitus (aOR, 1.07–1.33), and cancer (aOR, 1.42–1.36)<sup>8,22</sup>.

Male sex is another risk factor for pneumonia, but may be explained by lifestyle factors. For example, smoking is reported to be more common in males in the United States (males 13% vs. females 10%) and Europe (males 22% vs. females 15%)<sup>24,25</sup>. Another factor may be the different hormone profiles, which affect the inflammatory response to infection<sup>26</sup>.

Immunocompromise also affects the risk of pneumonia<sup>8,20</sup>. Increases in cancer survivorship, transplantation, and immunosuppressive drug use have increased the number of immunocompromised individuals in the population, with a recent study showing that 6.6% of adult population in the United States is immunocompromised<sup>17</sup>. Furthermore, observational studies in the United States and Europe have reported immunocompromise in approximately 10% and 20% of people with pneumonia, respectively<sup>19,20</sup>. The main challenge for clinicians is the lack of a specific definition for immunocompromise, which represents a heterogeneous spectrum of clinical conditions. In an effort to identify immunocompromised hosts, the American Thoracic Society (ATS) recently published a working definition for use in practice<sup>18</sup>.

Other risk factors to consider are higher alcohol consumption<sup>27</sup>, being underweight, living conditions (e.g., large households or regular contact with children), air pollution, and others<sup>8,28</sup>.

## PROGNOSIS IN CAP

Decisions about where to treat CAP depend on disease severity, comorbidities, the presence of hypoxemia, and likely treatment

adherence. The severity of disease is primarily assessed through clinical judgment, supported by the use of severity scales, such as the Pneumonia Severity Index (PSI) and the CURB-65 score, that predict the risk of mortality<sup>29</sup>. However, these severity scores are limited in their usefulness for identifying patients who require admission to ICU, especially due to the high weighting given to age in both scales and the low weighting given to variables such as respiratory failure and other organic dysfunctions<sup>30</sup>. For immunocompromised patients, the decision should be based on clinical judgment, as no specific severity thresholds have been defined for this heterogeneous patient population. The severity of CAP and the clinical course of patients during initial hospitalization affect short- and long-term survival. One study in the United States compared 1-year mortality rates between populations hospitalized with CAP and severe CAP or a poor clinical course (e.g., requiring ICU admission) versus populations with CAP who had a favorable clinical course (e.g., who achieved early clinical stability). The 1-year mortality rate for the overall CAP population was 30%, but this increased to 47% for patients who required ICU admission and decreased to 24% for patients who achieved early clinical stability<sup>31</sup>.

The ATS/Infectious Diseases Society of America (ATS/IDSA) guideline recommendations for ICU admission continue to be to use the minor and major diagnostic criteria proposed in 2007 to define patients with severe CAP<sup>32</sup>. Major criteria identify patients who require immediate ICU care, whereas minor criteria identify patients who are more likely to require ICU care and benefit from more aggressive therapy or closer observation. This

recommendation is based on validation of these criteria across several studies<sup>33,34</sup>.

A recent prospective study has validated the ATS/IDSA criteria used in elderly patients hospitalized with CAP<sup>35</sup>. The study found that 26% of patients met the criteria for severe CAP and 10% required ICU care. The ATS/IDSA criteria showed moderate accuracy in predicting ICU admission, with 79% agreement, a sensitivity of 75%, and a specificity of 80%. Patients on invasive mechanical ventilation were always admitted to the ICU, whereas almost half of the patients with septic shock did not require ICU care. Patients with septic shock in the ICU had a lower 30-day mortality compared with patients treated in wards (30% vs. 60%). However, elderly patients with severe CAP, but without major negative criteria, had similar mortality whether treated in the ICU or ward. The study concluded that the ATS/IDSA criteria are moderately effective in predicting ICU admission in elderly patients, with patients meeting the older criteria (e.g., septic shock and invasive mechanical ventilation) benefiting from ICU care, while others can be effectively managed on the ward.

A recently published study compared the ability of a casual probabilistic network model, SepsisFinder-Machine Learning (SeF-ML), to predict 30-day mortality in CAP against other severity scores, including CURB-65, PSI, Sequential Organ Failure Assessment (SOFA) score, and quick SOFA (qSOFA). Using a derivation cohort (d) of 4531 patients and a validation cohort (v) of 1034 patients, area under the receiver operating characteristic curve (AUC) calculations showed that SeF-ML (AUC-d, 0.801; AUC-v,

0.826) outperformed the CURB-65 (AUC-d, 0.759; AUC-v, 0.764), SOFA (AUC-d, 0.671; AUC-v, 0.771), and qSOFA (AUC-d, 0.642; AUC-v, 0.729) scores. However, the SeF-ML did not differ significantly from the PSI (AUC-d, 0.799; AUC-v, 0.830)<sup>36</sup>. These results suggest the potential of artificial intelligence as a future tool for supporting mortality prediction in patients with CAP.

Severe CAP remains the most important reason for ICU care. Very old patients with multiple comorbidities are at increased risk of severe pneumonia and 10% to 20% of patients with CAP are reported to have a clinical condition associated with immunosuppression. These features represent important challenges in patient care and achieving the best outcome possible. Severity scores should be used as an adjunct tool and should not replace clinical judgment.

## MICROBIAL ETIOLOGY AND ANTIMICROBIAL RESISTANCE

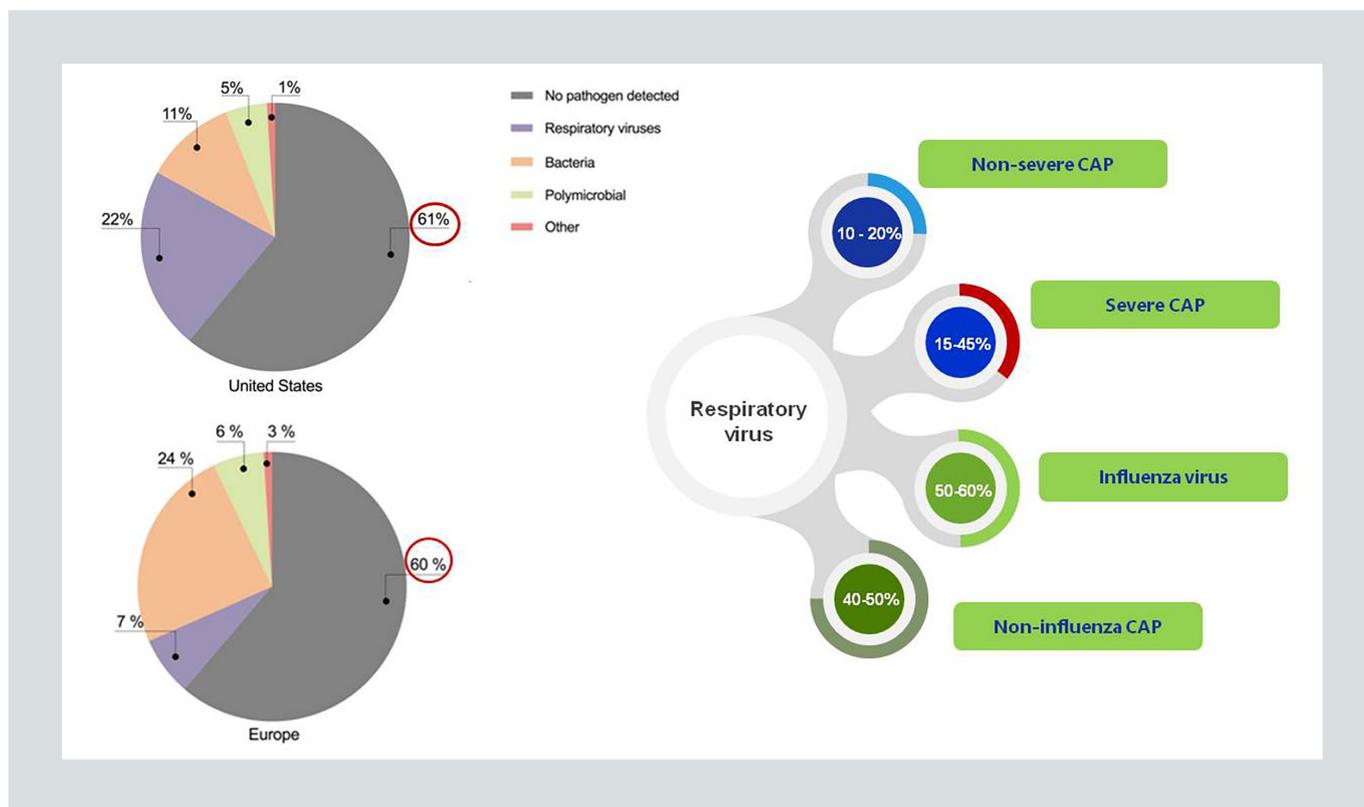
Several pathogens can cause pneumonia, but *Streptococcus pneumoniae* and respiratory viruses are the most frequent reported<sup>2</sup>. Observational studies from the United States show that respiratory viruses are the most frequently identified cause of CAP, with decreases in the incidence of *S. pneumoniae* attributed to the introduction of pneumococcal vaccination schedules and the decrease in the rate of smoking since 2000<sup>37</sup>. By contrast, European studies continue to identify *S. pneumoniae* as the main etiological agent (Fig. 3).

Recently published data on the epidemiology of pneumococcal pneumonia in the United

States reported an incidence of 93 hospitalizations per 100,000 adults, which would extrapolate to 226,696 annual hospitalizations<sup>38</sup>. Their data reported that serotypes 19A (12%), 3 (11%), and 22F (11%) were the most frequently identified. Notably, serotype 8 was the most frequent in patients requiring ICU admission, serotype 18C was associated with the presence of cardiac events, and serotype 1 was the most frequent in patients who died<sup>39</sup>. Data from a recently published British study of the trend in pneumococcal pneumonia over a 10-year period showed an increase from 36% in 2013 to 67% in 2023. The study also identified a noteworthy increase in the proportion of CAP cases attributed to serotype 3, which rose from 13% in 2013 to 49% in 2023. Older age, male sex, chronic kidney disease, and asthma were associated with the risk of CAP caused by serotype 3. Interesting data from a Spanish study into the 20-year trend in mortality associated with pneumococcal pneumonia reported an overall 30-day mortality of 8% that did not change significantly over time ( $p = 0.33$ ). However, the authors did observe a decrease in ICU mortality when comparing the first (26%) and second (10%) periods, although without statistical significance after adjustment ( $p = 0.38$ ).

Together, these results demonstrate the importance of *S. pneumoniae* in pneumonia and the relevance of a continuing to offer routine pneumococcal vaccination, especially in people at increased risk of pneumonia.

Respiratory viruses are identified in 10-20% of all adults hospitalized with CAP who have an established microbiological diagnosis<sup>2,7</sup>. In severe CAP, respiratory viruses are identified in 15-45% of cases (Fig. 3)<sup>2,37-41</sup>. Respiratory



**FIGURE 3.** Microbial etiology of CAP in Europe and the United States, and the proportion of respiratory virus according to severity and group of viruses.

virus is also identified in up to one-third of patients who develop sepsis<sup>39-41</sup>. The most frequent respiratory viruses identified in CAP are influenza A/B virus, RSV, rhinovirus, para-influenza virus, metapneumovirus, adenovirus, and coronaviruses<sup>2</sup>.

Influenza virus is identified in approximately one-third of patients hospitalized with severe pneumonia and requiring ICU admission. Among these, up to 50% may require mechanical ventilation due to acute respiratory distress syndrome and the mortality rate may reach 25%<sup>42</sup>. Another complication related to viral pneumonia is sepsis, which is reported in 19% of patients with CAP admitted to the ICU<sup>42</sup>. Cardiac events are another complication reported in severe influenza pneumonia<sup>42</sup>.

In viral CAP, an almost equal proportion of influenza and non-influenza respiratory viruses cause clinical disease<sup>42</sup>. Scientific evidence suggests that the complications and clinical course of patients with CAP due to non-influenza and influenza viruses are similar. Zhou et al. reported that severity on admission, frequency of sepsis and hypoxemia, admission to ICU, need for mechanical ventilation, length of hospital stay, and mortality were comparable in patients with CAP caused by non-influenza and influenza virus<sup>43</sup>. These data demonstrate the importance of early identification of respiratory viruses and the need for further research to develop effective new antivirals. Antibiotic-resistant pathogens or product engagement score (PES) pathogens (PES is an acronym for

*Pseudomonas aeruginosa*, extended-spectrum  $\beta$ -lactamase-producing *Enterobacteriaceae*, and methicillin-resistant *Staphylococcus aureus* (MRSA) are identified in a small proportion (6%) of CAP cases. However, these pathogens appear to be twice as common in older adults (12%) when compared with the general population<sup>44,45</sup>. These data highlight the importance of knowing the risk factors for these pathogens and to identify cases early.

Several scores have been developed to identify antibiotic-resistant pathogens.

One example is the validated Drug Resistance in Pneumonia (DRIP) score<sup>46</sup>. This includes previous antibiotic use, residence in a long-term care facility, tube feeding, and prior infection by a drug-resistant pathogen (in the past year) as major risk factors (scoring 2 points each), and hospitalization (in the past 60 days), chronic pulmonary disease, poor functional status, gastric acid suppression, wound care, and MRSA colonization (in the past year) as minor risk factors (scoring 1 point each). A patient is considered to be at high risk of drug-resistant pathogens if they have a DRIP score  $\geq 4$  points<sup>46</sup>. An elevated DRIP score increases the recommendation to use broad-spectrum antibiotics, mainly because the score was more selective than the health-care-associated CAP criteria that are no longer recommended by international guidelines<sup>47</sup>.

Another tool is the PES score, which categorizes patients according to risk factors into three categories ( $\leq 1$  point, 2-4 points, and  $\geq 5$  points, indicating low, medium, and high risk of infection, respectively, by PES pathogens<sup>44</sup>). The scores for each variable included in the PES score are as follows: 1 point for

age 40-65 years and male sex; 2 points for age  $> 65$  years, prior antibiotic use, chronic respiratory disorders, and altered consciousness; 3 points for chronic renal failure; and minus 1 point if fever was present at onset. Two studies have validated the PES score in key populations (i.e., ward patients, ICU patients, and older adults). The validation in ward and ICU patients produced AUCs of 0.818 and 0.73, respectively, indicating good accuracy<sup>48</sup>. Validation in older adults with CAP produced an AUC of 0.64 for the PES score, indicating differences in clinical characteristics between the elderly and general population<sup>45</sup>.

## ANTIMICROBIAL TREATMENT OF CAP

The main recommendations of treatment guidelines are summarized in table 1, with detail provided in the following text. Clinical guidelines for the management of CAP recommend initiating empirical antimicrobial therapy based on the severity of infection and the presence of risk factors for antibiotic-resistant pathogens<sup>29</sup>.

In patients with severe pneumonia, studies show that using a  $\beta$ -lactam plus macrolide can reduce the length of hospital stay together with the in-hospital, ICU, and long-term mortality<sup>49-53</sup> (Table 1). Some of the reasons for the beneficial effects of macrolides in severe pneumonia include their immunomodulatory properties, biofilm disrupting ability, quorum sensing ability, pneumolysin reduction effect, and atypical bacteria coverage<sup>54</sup>. Therefore, recent guidelines for severe CAP recommend combination therapy with a  $\beta$ -lactam plus macrolide<sup>55</sup>.

TABLE 1. Main recommendations for the antimicrobial treatment of CAP patients

Treatment	Non-severe CAP	Severe CAP
Empiric therapy	$\beta$ -lactam + macrolide. Fluoroquinolone only if confirmed allergy	$\beta$ -lactam + macrolide. If macrolide is not tolerated, replace with fluoroquinolone
Anti-MRSA therapy. When necessary, use vancomycin or linezolid	Only start if there is previous respiratory isolation of MRSA or risk factors and a culture positive for MRSA	Start parenteral antibacterial drugs if previous respiratory isolation of MRSA or recent hospitalization
Anti-pseudomonal therapy. Cefepime may be preferred to piperacillin-tazobactam when necessary. Alternative agents: Ceftazidime, imipenem, or meropenem	Only if previous respiratory isolation of <i>P. aeruginosa</i> or risk factors and a positive culture result	Start parenteral antibacterial drugs if previous respiratory isolation of <i>P. aeruginosa</i> or recent hospitalization
Corticosteroids	Do not use	Use in severe CAP: (1) mechanical ventilation; (2) high-flow nasal cannula with a $\text{PaO}_2/\text{FiO}_2$ ratio < 300, with $\text{FiO}_2 \geq 50\%$ ; (3) PSI > 130
Antiviral treatment	If high suspicion of influenza, start antiviral therapy while awaiting the results of diagnostic tests	If high suspicion of influenza, start antiviral therapy while awaiting the results of diagnostic tests

CAP: community-acquired pneumonia; MRSA: methicillin-resistant *Staphylococcus aureus*; PSI: Pneumonia Severity Index; *P. aeruginosa*: *Pseudomonas aeruginosa*. Based on 2019 IDSA/ATS guidelines for CAP management.

In hospitalized patients with documented influenza virus, current guidelines recommend using an anti-influenza agent, such as oseltamivir, regardless of the illness duration. However, evidence shows that the benefit of oseltamivir is greatest within the first 48 h of infection onset. Therefore, in patients with a high suspicion of influenza, antiviral therapy should be initiated while awaiting diagnostic test results<sup>29</sup>. Notably, a large retrospective study of 166,268 patients with CAP from 179 hospitals in the United States reported that only 23% were tested for influenza virus, of whom 12% tested positive<sup>56</sup>. The study showed an increase in testing from 15% in 2010 to 36% in 2015, with testing levels reaching 29% during the influenza season (October-May) compared with just 8% during outside the influenza season (June-September). Consistent with the guideline recommendations, a positive influenza test result was associated with antiviral

treatment, with early treatment being associated with lower mortality<sup>56</sup>. These results suggest that more widespread influenza virus testing could improve patient outcomes.

Oseltamivir is the recommended first-line treatment for severe influenza infection and in patients at risk of complications<sup>29,57</sup>. It is active against influenza A and B viruses, but not against other respiratory viruses<sup>58</sup>. The timing of antiviral treatment initiation is critical to optimal outcomes. Initiating treatment within 2 days of symptom onset or hospitalization appears to be most effective, although benefits may still be observed when treatment is initiated up to 4-5 days after symptom onset<sup>29</sup>.

Current treatments for SARS-CoV-2 include antivirals such as remdesivir<sup>59,60</sup>, nirmatrelvir and ritonavir, and molnupiravir, as well as adjunctive corticosteroid therapy. In December 2022, the United States Food and Drug

Administration approved the emergency use of Paxlovid, a proprietary combination of nirmatrelvir and ritonavir, for the oral treatment of mild-to-moderate coronavirus disease 19 (COVID-19) in patients ages  $\geq 12$  years of age who weighed at least 40 kg and were at high risk of progressing to severe COVID-19. Evidence shows that remdesivir is most effective against COVID-19 in patients with earlier disease who do not require mechanical ventilation or extracorporeal membrane oxygenation.

Ribavirin and palivizumab are used to treat severe RSV infection<sup>61,62</sup>. Concerning the use of corticosteroids in severe CAP, the 2019 ATS/IDSA guideline recommends against routine use because the available evidence from meta-analyses at the time of writing did not consistently demonstrate mortality benefits<sup>29,63,64</sup>. More recently published guidelines for severe CAP recommend corticosteroid use in the presence of shock<sup>55</sup>. This recommendation stands even when taking into account that a recent randomized study of 584 patients with severe CAP showed no benefit from the use of methylprednisolone on 60-day mortality (OR, 0.9; 95% CI 0.57-1.4)<sup>65</sup>. The evaluation of corticosteroid use in six clinical trials showed reductions in ICU mortality (risk ratio [RR], 0.36; 95% CI, 0.16-0.82), the incidence of septic shock, and the requirement for mechanical ventilation, without major adverse effects<sup>66</sup>. The most significant evidence for the benefit of corticosteroids in severe pneumonia was published in 2023 with the results of the CAPE-COD study<sup>67</sup>. That trial included 795 patients admitted to ICU without septic shock and randomized them to receive either placebo or 200 mg of hydrocortisone daily for 4-7 days according to clinical response. The intervention group

had lower 28-day mortality (6.2% vs. 11.9%,  $p = 0.006$ ) and there was less use of intubation and vasopressors<sup>67</sup>.

Several systematic reviews and meta-analyses have shown a relationship between corticosteroid use for influenza infection and higher mortality rates in patients with severe influenza infection<sup>68,69</sup>. A meta-analysis published in 2019, which included ten trials that evaluated 6548 patients with influenza pneumonia, reported a mortality RR of 1.75 for patients treated with corticosteroids<sup>70</sup>. The results were similar when only including patients with H1N1 influenza (RR, 1.61). Furthermore, patients who received corticosteroids had longer ICU stays (median increase of 2.14 days), while patients who did not receive corticosteroids had a higher proportion of secondary bacterial infections (RR 1.98). The worse outcomes observed in patients who received corticosteroids may reflect prolonged viremia due to immunosuppression, higher rates of secondary infections, or other adverse events associated with corticosteroid use. Previous observational studies have reported that corticosteroids may prolong influenza viral replication and viremia<sup>71</sup>. Current clinical guidelines advise against the routine use of systemic corticosteroids in influenza virus infection.

By contrast, dexamethasone is recommended in COVID-19 when patients require oxygen therapy, including mechanical ventilation<sup>72,73</sup>. Data from the RECOVERY trial showed that 6 mg/day dexamethasone for 10 days in patients with COVID-19 requiring oxygen therapy resulted in a 28-day mortality of 29%, which compared favorably with the 41% mortality observed in the routine care group<sup>74</sup>.

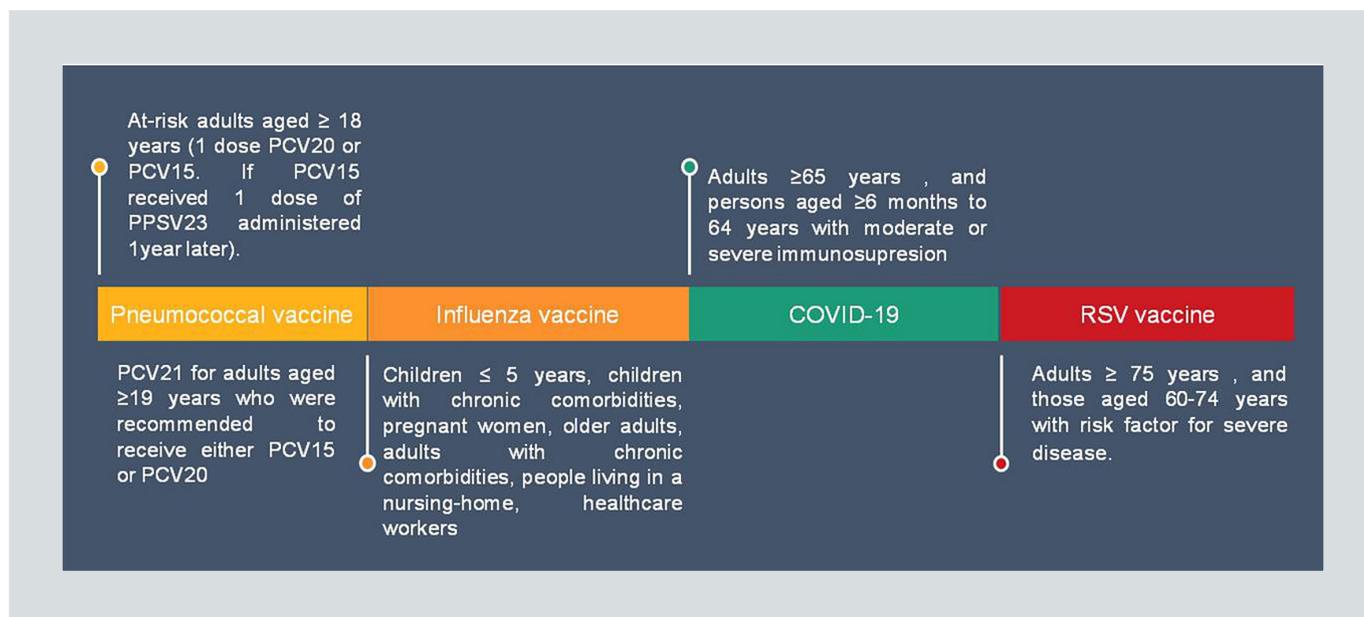


FIGURE 4. Main recommendations for vaccination against pneumococcus, influenza virus, SARS-CoV-2 and RSV.

However, no benefit was seen in patients not requiring oxygen, with 28-day mortality of 18% and 14% for the dexamethasone and routine care groups, respectively.

## PREVENTION

Vaccination remains the main strategy to prevent pneumonia and protect patients at risk of bacteria and viruses that cause lung infection (Fig. 4). The Advisory Committee on Immunization Practices (ACIP) recommends pneumococcal vaccination for at-risk adults ages  $\geq 18$  years, such as one dose of the PCV20 or the PCV15. If a patient receives PCV15, a dose of PPSV23 should be administered 1 year later<sup>75</sup>. The ACIP recommend PCV21 as an option for adults ages  $\geq 19$  years who are recommended to receive either PCV15 or PCV20<sup>76</sup>. More recently (October 23, 2024), the ACIP recommended lowering the age of pneumococcal vaccination from 65 to 50 years old, aiming to protect more adults<sup>77</sup>.

The Centers for Disease Control and Prevention recommends that everyone age 6 months and older should receive the influenza vaccine. However, this vaccine is especially important for people at higher risk of serious complications, who live with or care for people at a higher risk of serious complications, and all people working in health care settings<sup>78</sup>. In European countries, influenza vaccine is recommended for children under 5 years old, pregnant women, older adults, people with chronic comorbidities, people living in nursing homes, and healthcare workers<sup>79</sup>.

On October 23, 2024, the ACIP recommended the COVID-19 vaccine for adults aged 65 years and over, for persons aged 6 months to 64 years with moderate or severe immunosuppression of at least 2 months' duration<sup>80</sup>.

The ACIP recommends RSV vaccination for all adults ages 75 years and over, as well as a single dose of the vaccine for those ages 60-74

years with risk factors for severe disease. The risk factors related to severe RSV disease include chronic comorbidities, such as lung disease, cardiovascular disease, diabetes mellitus, and neurological disease, as well as immunosuppression, frailty, advanced age, and nursing home residence<sup>81</sup>.

## CONCLUSION

CAP remains the leading infectious cause of death worldwide. *S. pneumoniae* and respiratory viruses remain the main pathogens identified in pneumonia. Drug-resistant pathogens are uncommon in the general population but occur at higher rates among older adults. Influenza pneumonia has different clinical characteristics and a more challenging management in the older population. Overall mortality remains high despite advances in the diagnosis and management of patients with severe CAP, especially in patients who require invasive mechanical ventilation. Pneumonia survivors also frequently suffer both short- and long-term complications. Vaccines are an important tool for preventing pneumonia, but there is an urgent need to increase awareness about the importance of vaccination, especially in people at risk of severe infection.

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## CONFLICTS OF INTEREST

None.

## ETHICAL CONSIDERATIONS

**Protection of humans and animals.** The authors declare that no experiments involving humans or animals were conducted for this research.

**Confidentiality, informed consent, and ethical approval.** The study does not involve patient personal data nor requires ethical approval. The SAGER guidelines do not apply.

**Declaration on the use of artificial intelligence.** The authors declare that no generative artificial intelligence was used in the writing of this manuscript.

## REFERENCES

1. GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the global burden of disease study 2021. *Lancet*. 2024;403:2100-32.
2. Torres A, Cilloniz C, Niederman MS, Menéndez R, Chalmers JD, Wunderink RG, et al. Pneumonia. *Nat Rev Dis Primers*. 2021;7:25.
3. Cillóniz C, Dominedò C, Pericàs JM, Rodríguez-Hurtado D, Torres A. Community-acquired pneumonia in critically ill very old patients: a growing problem. *Eur Respir Rev*. 2020;29:190126.
4. Feldman C, Anderson R. Pneumonia as a systemic illness. *Curr Opin Pulm Med*. 2018;24:237-43.
5. Restrepo MI, Reyes LF. Pneumonia as a cardiovascular disease. *Respirology*. 2018;23:250-9.
6. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet*. 2022;399:629-55.
7. Ramirez JA, Wiemken TL, Peyrani P, Arnold FW, Kelley R, Mattingly WA, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. *Clin Infect Dis*. 2017;65:1806-12.
8. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax*. 2013;68:1057-65.
9. CDC. Vaccination Coverage among Adults in the United States, National Health Interview Survey, 2022. Adult Vax View; 2024. Available from: <https://www.cdc.gov/adultvaxview/publications-resources/adult-vaccination-coverage-2022.html> [Last accessed on 2025 Jan 06].
10. WHO European Health Information at your Fingertips. Available from: [https://gateway.euro.who.int/en/indicators/epw\\_29-pneumococcal-vaccination-coverage](https://gateway.euro.who.int/en/indicators/epw_29-pneumococcal-vaccination-coverage) [Last accessed on 2025 Jan 06].
11. CDCTobaccoFree. Burden of Tobacco Use in the U.S. Centers for Disease Control and Prevention; 2024. Available from: <https://www.cdc.gov/tobacco/campaign/tips/resources/data/cigarette-smoking-in-unit-ed-states.html> [Last accessed on 2025 Jan 06].

12. Overview - European Commission; 2024. Available from: <https://health.ec.europa.eu/tobacco/overview-en> [Last accessed on 2025 Jan 06].
13. Lopardo GD, Fridman D, Raimondo E, Albornoz H, Lopardo A, Bagnulo H, et al. Incidence rate of community-acquired pneumonia in adults: a population-based prospective active surveillance study in three cities in South America. *BMJ Open*. 2018;8:e019439.
14. HIV/AIDS | WHO | Regional Office for Africa; 2025. Available from: <https://www.afro.who.int/health-topics/hivaids> [Last accessed on 2025 Jan 11].
15. JustActions. The Missing Piece: why the global pandemic is an inflection point for pneumonia control. 2021;
16. Harpaz R, Ortega-Sanchez IR, Seward JF, Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC). Prevention of herpes zoster: recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep*. 2008;57:1-30; quiz CE2-4.
17. Martinson ML, Lapham J. Prevalence of immunosuppression among US adults. *JAMA*. 2024;331:880-2.
18. Cheng GS, Crothers K, Aliberti S, Bergeron A, Boeckh M, Chien JW, et al. Immunocompromised host pneumonia: definitions and diagnostic criteria: an official American thoracic society workshop report. *Ann Am Thorac Soc*. 2023;20:341-53.
19. Ramirez JA, Chandler TR, Furmanek SP, Carrico R, Wilde AM, Sheikh D, et al. Community-acquired pneumonia in the immunocompromised host: epidemiology and outcomes. *Open Forum Infect Dis*. 2023;10:ofad565.
20. Di Pasquale MF, Sotgiu G, Gramegna A, Radovanovic D, Terraneo S, Reyes LF, et al. Prevalence and etiology of community-acquired pneumonia in immunocompromised patients. *Clin Infect Dis*. 2019;68:1482-93.
21. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373:415-27.
22. Almirall J, Serra-Prat M, Bolibar I, Balasso V. Risk factors for community-acquired pneumonia in adults: a systematic review of observational studies. *Respiration*. 2017;94:299-311.
23. Weir DL, Majumdar SR, McAlister FA, Marrie TJ, Eurich DT. The impact of multimorbidity on short-term events in patients with community-acquired pneumonia: prospective cohort study. *Clin Microbiol Infect*. 2015;21:264.e7-13.
24. CDCTobaccoFree. Burden of Tobacco Use in the U.S. Centers for Disease Control and Prevention; 2024. Available from: <https://www.cdc.gov/tobacco/campaign/tips/resources/data/cigarette-smoking-in-united-states.html> [Last accessed on 2025 Jan 16].
25. Where in Europe do People Smoke the most and the Least? Euronews. Available from: <https://www.euronews.com/health/2023/08/14/smoking-in-europe-which-countries-are-the-most-and-least-addicted-to-tobacco-and-vaping> [Last accessed on 2025 Jan 16].
26. Barbagelata E, Cilloniz C, Dominedò C, Torres A, Nicolini A, Solidoro P. Gender differences in community-acquired pneumonia. *Minerva Med*. 2020;111:153-65.
27. Samokhvalov AV, Irving HM, Rehm J. Alcohol consumption as a risk factor for pneumonia: a systematic review and meta-analysis. *Epidemiol Infect*. 2010;138:1789-95.
28. Neupane B, Jerrett M, Burnett RT, Marrie T, Arain A, Loeb M. Long-term exposure to ambient air pollution and risk of hospitalization with community-acquired pneumonia in older adults. *Am J Respir Crit Care Med*. 2010;181:47-53.
29. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American thoracic society and infectious diseases society of America. *Am J Respir Crit Care Med*. 2019;200:e45-67.
30. Waterer G. Severity scores and community-acquired pneumonia. Time to move forward. *Am J Respir Crit Care Med*. 2017;196:1236-8.
31. Furmanek S, Chandler T, Ramirez JC. Long term mortality in community-acquired pneumonia: incidence in special populations. *Norton Healthcare Med J*. 2024;1:2-9.
32. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44 Suppl 2:S27-72.
33. Salih W, Schembri S, Chalmers JD. Simplification of the IDSA/ATS criteria for severe CAP using meta-analysis and observational data. *Eur Respir J*. 2014;43:842-51.
34. Chalmers JD, Mandal P, Singanayagam A, Akram AR, Choudhury G, Short PM, et al. Severity assessment tools to guide ICU admission in community-acquired pneumonia: systematic review and meta-analysis. *Intensive Care Med*. 2011;37:1409-20.
35. Cilloniz C, Ferrer M, Pericàs JM, Serrano L, Méndez R, Gabarrús A, et al. Validation of IDSA/ATS guidelines for ICU admission in adults over 80 years old with community-acquired pneumonia. *Arch Bronconeumol*. 2023;59:19-26.
36. Cilloniz C, Ward L, Mogensen ML, Pericàs JM, Méndez R, Gabarrús A, et al. Machine-learning model for mortality prediction in patients with community-acquired pneumonia: development and validation study. *Chest*. 2023;163:77-88.
37. Association AL. Tobacco Trends Brief: Overall Tobacco Trends Brief. Available from: <https://www.lung.org/research/trends-in-lung-disease/tobacco-trends-brief/overall-smoking-trends> [Last accessed on 2025 Jan 4].
38. Ramirez J, Furmanek S, Chandler TR, Wiemken T, Peyrani P, Arnold F, et al. Epidemiology of pneumococcal pneumonia in Louisville, Kentucky, and its estimated burden of disease in the United States. *Microorganisms*. 2023;11:2813.
39. Cilloniz C, Dominedò C, Magdaleno D, Ferrer M, Gabarrús A, Torres A. Pure viral sepsis secondary to community-acquired pneumonia in adults: risk and prognostic factors. *J Infect Dis*. 2019;220:1166-71.
40. Ljungström LR, Jacobsson G, Claesson BE, Andersson R, Enroth H. Respiratory viral infections are underdiagnosed in patients with suspected sepsis. *Eur J Clin Microbiol Infect Dis*. 2017;36:1767-76.
41. Hartman L, Zhu Y, Edwards KM, Griffin MR, Talbot HK. Underdiagnosis of influenza virus infection in hospitalized older adults. *J Am Geriatr Soc*. 2018;66:467-72.
42. Cilloniz C, Luna CM, Hurtado JC, Marcos MÁ, Torres A. Respiratory viruses: their importance and lessons learned from COVID-19. *Eur Respir Rev*. 2022;31:220051.
43. Zhou F, Wang Y, Liu Y, Liu X, Gu L, Zhang X, et al. Disease severity and clinical outcomes of community-acquired pneumonia caused by non-influenza respiratory viruses in adults: a multicentre prospective registry study from the CAP-china network. *Eur Respir J*. 2019;54:1802406.
44. Prina E, Ranzani OT, Polverino E, Cilloniz C, Ferrer M, Fernandez L, et al. Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. *Ann Am Thorac Soc*. 2015;12:153-60.
45. Cilloniz C, Dominedo C, Peroni HJ, Di Giannatale P, Garcia-Vidal C, Gabarrus A, et al. Difficult to treat microorganisms in patients aged over 80 years with community-acquired pneumonia: the prevalence of PES pathogens. *Eur Respir J*. 2020;56:2000773.
46. Webb BJ, Dascomb K, Stenehjem E, Vikram HR, Agrwal N, Sakata K, et al. Derivation and multicenter validation of the drug resistance in pneumonia clinical prediction score. *Antimicrob Agents Chemother*. 2016;60:2652-63.
47. Babbal D, Sutton J, Rose R, Yarbrough P, Spivak ES. Application of the DRIP score at a veterans affairs hospital. *Antimicrob Agents Chemother*. 2018;62:e02277-17.
48. Ceccato A, Mendez R, Ewig S, De La Torre MC, Cilloniz C, Gabarrus A, et al. Validation of a prediction score for drug-resistant microorganisms in community-acquired pneumonia. *Ann Am Thorac Soc*. 2021;18:257-65.
49. Reyes LF, Garcia E, Ibáñez-Prada ED, Serrano-Mayorga CC, Fuentes YV, Rodríguez A, et al. Impact of macrolide treatment on long-term mortality in patients admitted to the ICU due to CAP: a targeted maximum likelihood estimation and survival analysis. *Crit Care*. 2023;27:212.
50. Gattarello S, Borgatta B, Solé-Violán J, Vallés J, Vidaur L, Zaragoza R, et al. Decrease in mortality in severe community-acquired pneumococcal pneumonia: impact of improving antibiotic strategies (2000-2013). *Chest*. 2014;146:22-31.

51. Peyrani P, Wiemken TL, Metersky ML, Arnold FW, Mattingly WA, Feldman C, et al. The order of administration of macrolides and beta-lactams may impact the outcomes of hospitalized patients with community-acquired pneumonia: results from the community-acquired pneumonia organization. *Infect Dis (Lond)*. 2018;50:13-20.
52. Okumura J, Shindo Y, Takahashi K, Sano M, Sugino Y, Yagi T, et al. Mortality in patients with community-onset pneumonia at low risk of drug-resistant pathogens: impact of  $\beta$ -lactam plus macrolide combination therapy. *Respirology*. 2018;23:526-34.
53. Sligl WI, Asadi L, Eurich DT, Tjosvold L, Marrie TJ, Majumdar SR. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care Med*. 2014;42:420-32.
54. Emmet O'Brien M, Restrepo MJ, Martin-Loeches I. Update on the combination effect of macrolide antibiotics in community-acquired pneumonia. *Respir Investig*. 2015;53:201-9.
55. Martin-Loeches I, Torres A, Nagavci B, Aliberti S, Antonelli M, Bassetti M, et al. ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. *Intensive Care Med*. 2023;49:615-32.
56. Deshpande A, Klompas M, Yu PC, Imrey PB, Pallotta AM, Higgins T, et al. Influenza testing and treatment among patients hospitalized with community-acquired pneumonia. *Chest*. 2022;162:543-55.
57. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al. Clinical practice guidelines by the infectious diseases society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infect Dis*. 2019;68:e1-47.
58. Sur M, Lopez MJ, Baker MB. Oseltamivir. In: *StatPearls*. Treasure Island, FL: StatPearls Publishing; 2021. Available from: <http://www.ncbi.nlm.nih.gov/books/nbk539909> [Last accessed on 2021 Jun 21].
59. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19 - final report. *N Engl J Med*. 2020;383:1813-26.
60. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, et al. Repurposed antiviral drugs for covid-19 - interim who solidarity trial results. *N Engl J Med*. 2021;384:497-511.
61. Fragkou PC, Moschopoulos CD, Karofylakis E, Kelesidis T, Tsiodras S. Update in viral infections in the intensive care unit. *Front Med (Lausanne)*. 2021;8:575580.
62. Dandachi D, Rodriguez-Barradas MC. Viral pneumonia: etiologies and treatment. *J Investig Med*. 2018;66:957-65.
63. Stern A, Skalsky K, Avni T, Carrara E, Leibovici L, Paul M. Corticosteroids for pneumonia. *Cochrane Database Syst Rev*. 2017;12:CD007720.
64. Briel M, Spoorenberg SM, Snijders D, Torres A, Fernandez-Serrano S, Meduri GU, et al. Corticosteroids in patients hospitalized with community-acquired pneumonia: systematic review and individual patient data metaanalysis. *Clin Infectious Dis*. 2018;66:346-54.
65. Meduri GU, Shih MC, Bridges L, Martin TJ, El-Solh A, Seam N, et al. Low-dose methylprednisolone treatment in critically ill patients with severe community-acquired pneumonia. *Intensive Care Med*. 2022;48:1009-23.
66. Jiang S, Liu T, Hu Y, Li R, Di X, Jin X, et al. Efficacy and safety of glucocorticoids in the treatment of severe community-acquired pneumonia: a meta-analysis. *Medicine (Baltimore)*. 2019;98:e16239.
67. Dequin PF, Meziani F, Quenot JP, Kamel T, Ricard JD, Badie J, et al. Hydrocortisone in severe community-acquired pneumonia. *N Engl J Med*. 2023;388:1931-41.
68. Martin-Loeches I, Torres A. Corticosteroids for CAP, influenza and COVID-19: when, how and benefits or harm? *Eur Respir Rev*. 2021;30:200346.
69. Rodrigo C, Leonardi-Bee J, Lansbury L, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. *Cochrane Database Syst Rev*. 2019;3:CD010406.
70. Ni YN, Chen G, Sun J, Liang BM, Liang ZA. The effect of corticosteroids on mortality of patients with influenza pneumonia: a systematic review and meta-analysis. *Crit Care*. 2019;23:99.
71. Wang Y, Guo Q, Yan Z, Zhou D, Zhang W, Zhou S, et al. Factors associated with prolonged viral shedding in patients with avian influenza a(h7n9) virus infection. *J Infect Dis*. 2018;217:1708-17.
72. Therapeutic Management. COVID-19 Treatment Guidelines. Available from: <https://www.covid19treatmentguidelines.nih.gov/therapeutic-management> [Last accessed on 2021 Apr 12].
73. Therapeutics and COVID-19: Living Guideline. Available from: <https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-therapeutics-2021.1> [Last accessed on 2021 Apr 12].
74. Recovery Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with covid-19. *N Engl J Med*. 2021;384:693-704.
75. Kobayashi M, Pilishvili T, Farrar JL, Leidner AJ, Gierke R, Prasad N, et al. Pneumococcal vaccine for adults aged  $\geq 19$  years: recommendations of the advisory committee on immunization practices, United States, 2023. *MMWR Recomm Rep*. 2023;72:1-39.
76. Kobayashi M, Leidner AJ, Gierke R, Farrar JL, Morgan RL, Campos-Outcalt D, et al. Use of 21-valent pneumococcal conjugate vaccine among U.S. adults: recommendations of the advisory committee on immunization practices - United States, 2024. *MMWR Morb Mortal Wkly Rep*. 2024;73:793-8.
77. CDC. CDC Recommends Lowering the Age for Pneumococcal Vaccination from 65 to 50 Years Old. *CDC Newsroom*; 2024. Available from: <https://www.cdc.gov/media/releases/2024/s1023-pneumococcal-vaccination.html> [Last accessed on 2025 Jan 6].
78. Influenza Vaccination: A Summary for Clinicians | CDC; 2024. Available from: <https://www.cdc.gov/flu/professionals/vaccination/vax-summary.html> [Last accessed on 2024 Jun 5].
79. Vaccine Scheduler ECDC. Available from: <https://vaccine-schedule.ecdc.europa.eu/scheduler/bydisease?selecteddiseaseid=15&selectedcountryid=bydisease=-1> [Last accessed on 2025 Jan 23].
80. Roper LE, Godfrey M, Link-Gelles R, Moulia DL, Taylor CA, Peacock G, et al. Use of additional doses of 2024-2025 covid-19 vaccine for adults aged  $\geq 65$  years and persons aged  $\geq 6$  months with moderate or severe immunocompromise: recommendations of the advisory committee on immunization practices - United States, 2024. *MMWR Morb Mortal Wkly Rep*. 2024;73:1118-23.
81. Britton A, Roper LE, Kotton CN, Hutton DW, Fleming-Dutra KE, Godfrey M, et al. Use of respiratory syncytial virus vaccines in adults aged  $\geq 60$  years: updated recommendations of the advisory committee on immunization practices - United States, 2024. *MMWR Morb Mortal Wkly Rep*. 2024;73:696-702.