Antibiotic therapy for bacterial pneumonia

Hideo Kato[1,2]*

Abstract

Pneumonia is a common infection in patients of all ages. Determining its etiology and selecting antibiotic therapy are challenging for physicians in both private practice and hospitals. Moreover, the coronavirus disease pandemic revealed the importance of prevention and treatment of secondary bacterial pneumonia in patients hospitalized with viral respiratory infections. This review focuses on the types of bacteria that cause pneumonia and provides new insights into antibiotic therapy for bacterial pneumonia. Moreover, it also reviews the current state of knowledge regarding secondary bacterial pneumonia.

Keywords Bacterial pneumonia, Antibiotic therapy, Ceftriaxone, Secondary bacterial pneumonia

Background

Pneumonia is a disease associated with a high morbidity and mortality rate worldwide, and the incidence is increasing, particularly in immunocompromised individuals, children, and older adults [1]. Pneumonia is defined as the presence of new lung infiltrates with clinical evidence that the infiltrate is of infectious origin, such as new onset of fever, purulent sputum, leukocytosis, and decline in oxygenation [2]. The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) categorize pneumonia as community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP), based on the timing of the acquisition [3].

CAP is an acute infection of the pulmonary parenchyma that is acquired outside healthcare facilities. HAP is not present at the time of hospital admission, but has an onset 48 h or more after hospital admission. A substantial proportion of cases of HAP is caused by antibiotic-resistant bacteria, and the prevalence of antibiotic resistance among cases of CAP is also increasing. The

incidence of CAP among adults is 14 cases per 1,000 per year [4], and over 50% of cases require hospitalization [5]. The World Health Organization reported that CAP accounts for 4 million deaths per year and 7% of the total annual mortality rate [6]. The economic burden of the CAP is also high, costing an estimated EUR 10.1 billion per year [7]. Similarly, HAP is the main cause of death from nosocomial infection, with an incidence of 5 to 10 cases per 1,000 hospital admissions [8] and an estimated mortality rate of 20–30% [9]. Therefore, bacterial pneumonia warrants attention because it not only threatens the health of individuals but also increases the burden on the national economy.

The microbial etiology of pneumonia includes both bacteria and viruses. During the 1918 H1N1 influenza A virus pandemic, over half the individuals with influenza developed secondary bacterial pneumonia [10]. Even though antibiotics have subsequently been developed, the incidence of secondary bacterial pneumonia remains high in patients with viral pneumonia, and results in increased disease severity. Viral pneumonia complicated by secondary bacterial pneumonia is associated with higher morbidity and mortality compared with viral pneumonia alone in older adults and patients with chronic illnesses [11].

*Correspondence:
Hideo Kato
hkato59@med.mie-u.ac.jp
[1]Department of Pharmacy, Mie University Hospital, Mie 514-8507, Japan
[2]Department of Clinical Pharmaceutics, Division of Clinical Medical Science, Mie University Graduate School of Medicine, Mie, Japan

Notwithstanding the considerable global impact, bacterial pneumonia is a particularly important health problem in Japan because its aging population. This review provides details on the types of bacteria that cause pneumonia and provides new insights into antibiotic therapy for bacterial pneumonia. Moreover, the current state of knowledge regarding secondary bacterial pneumonia is also reviewed.

Bacteria that cause pneumonia

Timely and accurate identification of the pathogens causing pneumonia is critical for the initiation of antibiotic therapy; however, identifying the causative pathogen is challenging in clinical settings [12]. The "gold standard" for determining the etiology is the detection of respiratory pathogens in specimens obtained directly from the lungs by bronchoalveolar lavage, pleural fluid sampling, lung biopsy, or aspiration [13]. Sputum and tracheal aspirates obtained from the lower respiratory tract have a high probability of contamination from by upper respiratory tract bacteria; therefore, pathogens from specimens distant from the site of infection, such as blood and urine, are preferred to sputum and tracheal aspirates. However, the test results from these specimens must be carefully interpreted because no diagnostic method applied to non-pulmonary specimens has both high sensitivity and specificity for identifying the pathogen [12].

Causative pathogens by country worldwide

There are a wide variety of pneumonia-related pathogens [14]. The most common causes of bacterial pneumonia are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus* [15]. In Spain, *S. pneumoniae* is the leading cause of bacterial pneumonia, accounting for 31.7% of all cases [16]. In the United Kingdom, *S. pneumoniae* is the most common species associated with pneumonia (30%), followed by *H. influenzae* (19%) [17].

Shoar et al. [18] conducted a systematic review of confirmed cases of pneumonia in adults in developed countries. The review included 146 articles that reported on a total 82,674 patients with pneumonia. *S. pneumoniae* was the most common cause of pneumonia during the entire study period, and was identified, in 33–50% of all cases regardless of the microbiological technique used for identification. *H. influenzae* was the second most common cause (7–16% of cases). In contrast to developed countries, the most common pathogen identified in a study of bacterial pneumonia in Ethiopia was *K. pneumoniae*, with an overall prevalence of 22.0%, followed by *S. pneumoniae* (17.0%), *S. aureus* (14.5%), *P. aeruginosa* (10.0%), and *E. coli* (9.8%) [19]. *K. pneumoniae* has also been reported to be the leading cause of bacterial pneumonia

in Cambodia (26.9%), Nepal (27.0%), and Nigeria (23.0%) [20–22]. Because of the differences among countries, routine screening to identify the pathogen is necessary for management of patients with suspected pneumonia to select appropriate antibiotic therapy and to prevent the emergence of antimicrobial resistance.

Causative pathogens in Japan

In Japan, surveillance of causative respiratory pathogens has been continuously conducted during three periods (1994–1997; 2001–2004; and 2008–2010). *S. pneumoniae* was the most common pathogen identified in all three periods (1994 −1997, 23.0%; 2001–2004, 23.8%; 2008–2010, 25.9%), with a prevalence similar to that reported in Western countries [23–25]. Recently, Fujikura et al. [26] conducted a systematic review on the epidemiology of pneumonia in Japan in which they reviewed all published studies and epidemiological surveys on the isolation of pathogens in patients with pneumonia in Japan. The authors identified 56 eligible articles reporting on a total of 17,095 cases of bacterial pneumonia. Similar to previous studies [23–25], *S. pneumoniae* was the most common pathogen (20.0%), followed by *H. influenzae* (10.8%). In patients with pneumonia requiring hospitalization, *S. pneumoniae* was also the most frequently isolated pathogen (16.2%), followed by *H. influenzae* (6.9%). Moreover, the prevalence of *S. pneumoniae* was similar in studies published before 2000 and those published after 2010.

Antibiotic-resistant *S. pneumoniae*

Antibiotic resistance is a major concern in selecting treatment for bacterial pneumonia [27]. Antibiotic resistance has become a problem due to the emergence and dissemination of antibiotic-resistant pathogens in hospitals and community settings, inappropriate antibiotic use, and the overconsumption of antibiotics [28]. In China and Ethiopia, most *S. pneumoniae* isolates are highly resistant to erythromycin, azithromycin, and clindamycin [29, 30]. In Japan, the Japanese Society of Chemotherapy, Japanese Association for Infectious Diseases, and Japanese Society for Clinical Microbiology have conducted nationwide surveillance of the antimicrobial susceptibility of bacterial respiratory pathogens isolated from patients with lower respiratory infections [31]. Forty-two medical institutions participated in the surveillance and 264 *S pneumoniae* strains were evaluated. All strains were susceptible to benzylpenicillin, with a minimum inhibitory concentration (MIC) of less than 2 mg/L. Among β-lactam antibiotics, the 90% MIC (MIC_{90}) results of cephems other than cefaclor, cefmetazole, and ceftazidime were 0.5–2 mg/L and those of carbapenems were less than 0.25 mg/L. The MIC_{90} results of fluoroquinolones were 0.06–4 mg/L, and the MICs of garenoxacin

and sitafloxacin against all strains were less than 1 mg/L. In contrast, strains resistant to macrolides and clindamycin were common, with MIC_{90} results of over 128 mg/L. The pattern of antibiotic resistance in *S. pneumoniae* is attributable to empirical antibiotic administration and poor adherence to treatment guidelines. Therefore, specific antibiotic therapy is fundamental to the management and control of bacterial pneumonia.

Antibiotic therapy

Antibiotic therapy for patients with suspected bacterial pneumonia should be appropriate and should be administered as early as possible. Current guidelines recommend the use of β-lactam and β-lactamase inhibitor combinations, especially sulbactam-ampicillin (SAM) and ceftriaxone, for the initial treatment of pneumonia [2, 32, 33]. However, because the diagnosis of pneumonia is uncertain in some cases, patients with suspected pneumonia are prescribed empiric antibiotic therapy prior to identification of a bacterial pathogen to prevent rapid clinical deterioration and the need for hospital admission.

Ceftriaxone vs. broad-spectrum antibiotics

Some prognostic guidelines recommend the use of piperacillin-tazobactam (TZP) and carbapenems for the treatment of hospitalized patients with pneumonia [34, 35]. TZP and carbapenems are needed in the treatment of severe or very severe pneumonia. However, a previous study has shown that broad-spectrum antibiotics such as TZP and carbapenems are used as an empiric treatment in 50–68% of patients hospitalized with pneumonia in Japan [36]. The use of these broad-spectrum antibiotics is associated with several problems. First, because broad-spectrum antibiotics have anti-anaerobic activity, the use of broad-spectrum antibiotic therapy could cause the emergence of *Clostridioides difficile* infections [37, 38]. The use of broad-spectrum antibiotics leads to an increase in antimicrobial resistance rates and medical costs. Thus, ceftriaxone, which could cover almost every pathogen causing pneumonia, is considered to be one of the most useful antibiotics in the treatment of pneumonia. A single-center retrospective study was conducted in patients with pneumonia to evaluate whether ceftriaxone is as effective as broad-spectrum antibiotics (TZP and carbapenems) for the treatment of pneumonia [39]. The 30-day mortality rate was 0% in both groups. There were no differences in the incidence of initial treatment failure (ceftriaxone vs. broad-spectrum antibiotics, 4.3% vs. 0%, $p=0.312$), inappropriate treatment (23.1% vs. 26.7%, $p=0.827$), mean duration of antibiotic therapy (12.3±7.4 days vs. 12.5±5.4 days, $p=0.928$), or mean length of hospital stay (17.0±13.4 days vs. 17.0±7.7 days, $p=0.980$) in the two groups. However, the medical costs were considerably higher in the broad-spectrum antibiotic group than in the ceftriaxone group (8,678 Japanese yen vs. 35,582 Japanese yen, $p<0.001$). These findings demonstrate that ceftriaxone is an effective treatment for pneumonia and is not inferior to broad-spectrum antibiotics.

Ceftriaxone vs. SAM

Ceftriaxone is the most commonly used antibiotic for the treatment of pneumonia because it requires less frequent administration than that of alternative antibiotics, does not require a dose adjustment in patients with mild and moderate impaired renal function, and is suitable for use as an alternative antibiotic in patients who are allergic to penicillin [40, 41]. Ceftriaxone has a spectrum of activity similar to that of SAM against the predominant bacterial pathogens that cause pneumonia [42] However, ceftriaxone does not target the full spectrum of oral anaerobes that cause pneumonia [34, 43]. To date, only one meta-analysis has provided comprehensive evidence of the effectiveness of antibiotics in the treatment of pneumonia [6]. However, the meta-analysis did not compare the effectiveness of ceftriaxone and SAM for the treatment of pneumonia. Hence, a meta-analysis was subsequently conducted to compare the effectiveness of ceftriaxone and SAM as the initial treatment for pneumonia [44]. Four studies were included in the meta-analysis. The four studies included a total of 390 patients who received ceftriaxone, and 604 patients who received SAM. There were no significant differences in mortality and clinical cure rates between patients receiving ceftriaxone and SAM (ceftriaxone vs. SAM: mortality, 5.6% vs. 11.4%, odds ratio (OR): 1.85, 95% confidence interval (CI): 0.57–5.96; clinical cure rate, 87.5% vs. 91.8%, OR: 1.08, 95% CI: 0.18–6.44). Therefore, the meta-analysis concluded that ceftriaxone was not inferior to SAM as an initial treatment for pneumonia. However, it is necessary to consider the use of SAM in patients who have an unfavorable clinical course with ceftriaxone therapy, because β-lactamase-positive strains have been detected in 80–85% of oral anaerobes associated with pneumonia [45].

Optimal dosing regimen of ceftriaxone

Ceftriaxone, a third-generation cephalosporin, has a long plasmatic half-life [46], and thus, it can be administered once daily [47]. A 2 g dose administered once daily is frequently used in clinical settings [48, 49]. However, the Sanford Guide for Antimicrobial Therapy [50] suggests administering a 1 g dose of ceftriaxone twice daily. Recently, a single-center retrospective study and a basic study compared the effectiveness and safety of ceftriaxone administered as either a 1 g dose twice daily or a 2 g dose once daily, for the treatment of pneumonia [51, 52].

In a retrospective study [51], 61 patients were included (1 g twice daily, $n=33$; 2 g once daily, $n=28$). Only five patients receiving 1 g twice daily failed treatment for pneumonia, with a significant difference between the two dosing regimens (1 g administered twice daily vs. 2 g administered once daily, 15.2% vs. 0%, $p=0.032$). The percentages of patients who were afebrile (defined as a body temperature [BT] <37.0 ℃) and had C-reactive protein (CRP) levels <60% of the baseline at the end of therapy were higher in patients who received 2 g once daily than in those who received 1 g twice daily (afebrile, 45.5% vs. 78.3%, $p=0.014$; decreased CRP level, 25.0% vs. 60.7%, $p=0.005$). Moreover, changes in white blood cell (WBC) count, BT, and CRP levels were investigated for 2 weeks after the initiation of ceftriaxone therapy. Patients who received 2 g once daily showed significant decreases in WBC, BT, and CRP from 4 to 7 day after the initiation of ceftriaxone therapy, while patients who received 1 g twice daily showed significant decreases in BT and CRP from 4 to 7 days and 8–14 days, respectively. And CRP level and BT on 4–7 day in patients who received 2 g once daily were significantly lower than those in patients who received 1 g twice daily (2 g once daily vs. 1 g twice daily: CRP, 7.7 ± 6.2 mg/dL vs. 5.3 ± 4.1 mg/dL, $p=0.037$; body temperature, 37.3 ± 0.7 ℃ vs. 37.1 ± 0.6 ℃, $p=0.052$). In contrast, the percentage of patients with abnormal liver function test results did not differ significantly between the two dosing regimens. However, the percentage of patients diagnosed with choleliths during ceftriaxone therapy was higher in those who received 2 g once daily than in those who received 1 g twice daily (31.3% vs. 9.1%; $p=0.174$).

In a basic science study [52], the antimicrobial activities of two dosing regimens against *S. pneumoniae* with MICs of 1, 2, and 4 mg/L, were assessed using a murine model of pneumonia. The 2 g once daily regimen showed significantly higher antimicrobial activity against *S. pneumoniae* with MICs of 1 and 2 mg/L compared with the 1 g twice daily regimen (1 mg/L, -5.14 ± 0.19 $\Delta\log_{10}$ colony-forming unit (cfu)/lungs vs. -3.47 ± 0.17 $\Delta\log_{10}$ cfu/lungs, $p<0.001$; 2 mg/L, -3.41 ± 0.31 $\Delta\log_{10}$ cfu/lungs vs. -2.71 ± 0.37 $\Delta\log_{10}$ cfu/lungs, $p=0.027$). In contrast, no significant difference in antimicrobial activity was observed against *S. pneumoniae* with a MIC of 4 mg/L between the two dosing regimens (-0.33 ± 0.18 $\Delta\log_{10}$ cfu/lungs versus -0.42 ± 0.37 $\Delta\log_{10}$ cfu/lungs, $p=0.684$).

These studies demonstrated that a 2 g once daily regimen of ceftriaxone showed an improvement of clinical responses and early reduction of inflammatory markers and that the 2 g once daily regimen was effective in a murine model of pneumonia caused by *S. pneumoniae* with a MIC of ≤2 mg/L. Therefore, the 2 g once daily regimen was concluded to be a favorable dosing regimen for the initial treatment of pneumonia.

Secondary bacterial pneumonia following viral pneumonia

Causative bacterial pathogens

It was recently reported that the proliferation of viruses in lung tissues creates a suitable environment for bacterial pathogen colonization [53]. The onset of secondary bacterial pneumonia may cause a worsening of the patient's clinical condition [54]. To date, *S. pneumoniae* has been the predominant bacterial pathogen associated with influenza virus pandemics, accounting for one-quarter to one-half of severe and fatal cases [11, 55–57]. In patients with coronavirus disease 2019 (COVID-19), *S. pneumoniae* is also the most common cause of secondary bacterial pneumonia [54]. *S. pneumoniae* is a common part of the nasopharyngeal flora, with a prevalence of colonization of 40–95% in infants and 10–25% in adults [58]. Therefore, antibiotic therapies targeting *S. pneumoniae* should be considered in patients with secondary bacterial pneumonia.

Strategy of antibiotic therapy

The likelihood of combined viral and bacterial pneumonia is low in patients with mild-to-moderate viral pneumonia, and antibiotics can be safely withheld [59]. In the absence of supporting evidence of bacterial pneumonia, antibiotics should not be initiated even in patients with progressive respiratory distress [59]. However, data regarding the role of secondary bacterial pneumonia in acute respiratory decompensation are limited. Therefore, guideline-driven empirical antibiotic use may be reasonable until secondary bacterial pneumonia has been ruled out [59]. Of patients hospitalized with viral pneumonia, 56.6% have been reported to be treated with early empirical antibiotics [60]. In our hospital, ceftriaxone is recommended as an initial antibiotic therapy in patients hospitalized with COVID-19. A study has shown that ceftriaxone therapy is effective and safe in patients hospitalized with COVID-19 (under review). However, current studies provide insufficient evidence to support the routine use of antibiotics in patients hospitalized with COVID-19 [61]. Therefore, further research is needed to establish the most appropriate antibiotic therapy for the prevention and treatment of secondary bacterial pneumonia in patients with COVID-19.

Prevention of bacterial pneumonia

Prevention may be the best approach to the management of secondary bacterial pneumonia. Vaccination is the preferred means to prevent pneumonia. Seasonal vaccination with inactivated influenza vaccine has been shown to decrease the incidence of hospitalization and death due to pneumonia [62], and the use of a conjugate pneumococcal vaccine has been shown to prevent viral lower respiratory tract infections [62]. However, the

development of mutations and new subtypes in has weakened the effectiveness of vaccination of *S. pneumoniae*, influenza, and COVID-19. Therefore, the development of new methods to prevent the onset of pneumonia and alleviate its severity are urgently needed.

Conclusions

Because bacterial and viral pneumonia have high mortality rates, knowledge of possible pathogens and their therapeutic implications is essential for providing adequate antibiotic therapy. In developed countries, including Japan, *S. pneumoniae* is the leading cause of both primary and secondary bacterial pneumonia; therefore, broad-spectrum antibiotics effective against *S. pneumoniae* need to be considered in the initial treatment of bacterial pneumonia. An optimal dosing regimen for the initial treatment of pneumonia with ceftriaxone, which is one of the antibiotics recommended in the guidelines, has been established, and ceftriaxone has been shown to be effective and safe. However, further research is required to establish a new, better approaches for preventing secondary bacterial pneumonia.

Abbreviations

ATS	American Thoracic Society
BT	body temperature
CAP	community-acquired pneumonia
cfu	colony-forming unit
CI	confidence interval
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
HAP	hospital-acquired pneumonia
IDSA	Infectious Diseases Society of America
MIC	minimum inhibitory concentration
OR	odds ratio
SAM	sulbactam-ampicillin
TZP	piperacillin-tazobactam
WBC	white blood cell

Author contributions
HK wrote the manuscript, and read and approved the final manuscript.

Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The author declares that he has no competing interests.

References
1. Sampson S, De Pietro M. What to know about bacterial pneumonia. 2022.
2. American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA). Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2005;171:388–416.
3. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated Pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63:e61–111.
4. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax. 2013;68(11):1057–65.
5. Almirall J, Serra-Prat M, Bolíbar I, Balasso V. Risk factors for community-acquired pneumonia in adults: a systematic review of observational studies. Respiration. 2017;94(3):299–311.
6. Bai F, Li X. Comparing several treatments with antibiotics for community-acquired pneumonia: a systematic review and meta-analysis of randomized controlled trials. Iran J Public Health. 2021;50(6):1108–19.
7. Marshall DC, Goodson RJ, Xu Y, Komorowski M, Shalhoub J, Maruthappu M, et al. Trends in mortality from pneumonia in the Europe union: a temporal analysis of the European detailed mortality database between 2001 and 2014. Respir Res May. 2018;4(1):81.
8. Bassetti M, Righi E, Vena A, Graziano E, Russo A, Peghin M. Risk stratification and treatment of ICU acquired pneumonia caused by multidrug-resistant/extensively drug-resistant/pandrug-resistant bacteria. Curr Opin Crit Care. 2018;24:385–93.
9. Barbier F, Andremont A, Wolff M, Bouadma L. Hospital-acquired pneumonia and ventilator-associated pneumonia: recent advances in epidemiology and management. Curr Opin Pulm Med. 2013;19:216–28.
10. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis. 2008;198:962–70.
11. Sumitomo T, Kawabata S. Respiratory tract barrier dysfunction in viral-bacterial co-infection cases. Jpn Dent Sci Rev. 2024;60:44–52.
12. Meyer S. Challenges and progress toward determining pneumonia etiology. Clin Infect Dis. 2020;71:514–6.
13. Bradley JS, Byington CL, Shah SS, Alverson B, Carter ER, Harrison C, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. Clin Infect Dis. 2011;53:e25–76.
14. Shilpa A, Anuradha K, Venkatesha D. Drug susceptibility pattern of aerobic bacterial isolates from pulmonary infection in HIV seropositives and their correlation with CD4 count. IOSR J Dent Med Sci. 2014:13:37–41.
15. López-Palomo C, Martin-Zamorano M, Benitez E, Fernandez-Gutierrez C, Guerrero F, Rodriguez-Iglesias M, et al. Pneumonia in HIV-infected patients in the HAART era: incidence, risk, and impact of the pneumococcal vaccination. J Med Virol. 2004;72(4):517–24.
16. Curran A, Falco V, Crespo M, Martinez X, Ribera E, del Saz SV, et al. Bacterial pneumonia in HIV-infected patients: use of the pneumonia severity index and impact of current management on incidence, aetiology and outcome. HIV Med. 2008;9(8):609–15.
17. Taylor JK, Fleming GB, Singanayagam A, Hill AT, Chalmers JD. Risk factors for aspiration in community-acquired pneumonia: analysis of a hospitalized UK cohort. Am J Med. 2013;126:995–1001.
18. Shoar S, Musher DM. Etiology of community-acquired pneumonia in adults: a systematic review. Pneumonia (Nathan). 2020;12:11.
19. Tilahun M, Belete MA, Gedefie A, Debash H, Alemayehu E, Gebretsadik D et al. Etiology of bacterial pneumonia and multidrug resistance pattern among pneumonia suspected patients in Ethiopia: a systematic review and meta-analysis. 2024;24:182.
20. Rammaert B, Goyet S, Beaute J, Hem S, Te V, Try TP, et al. Klebsiella pneumoniaerelated community-acquired acute lower respiratory infections in Cambodia: clinical characteristics and treatment. BMC Infect Dis. 2012;12(1):1–7.

21. Khushbu Y, Satyam P. Bacteriological Profile of Lower respiratory tract infection (LRTI) among HIV seropositive cases in Central Terai of Nepal. Int J Curr Microbiol App Sci. 2015;4(11):431–42.

22. Urama EU, Ifeoma BE, Ifeanyi OO, Benedictta CO, Uchechukwu G. Microbiological Profile of respiratory tract infections among HIV Sero-positive subjects attending Nnamdi Azikiwe University Teaching Hospital Nnewi, Nigeria. Amer J Med Med Sci. 2018;8:37–42.

23. Ishida T, Hashimoto T, Arita M, Ito I, Owasa M. Etiology of community-acquired pneumonia in hospitalized patients: a 3-year prospective study in Japan. Chest. 1998;114:1588–93.

24. Ishida T, Hashimoto T, Arita M, Ito I, Owasa M. A 3-year prospective study of a urinary antigen-detection test for Streptococcus pneumoniae in community-acquired pneumonia: utility and clinical impact on the reported etiology. J Infect Chemother. 2004;10:359–63.

25. Umeki K, Takimatsu I, Yasuda C, Iwata A, Yoshioka D, Ishii H, et al. Clinical features of healthcare-associated pneumonia(HCAP)in a Japanese community hospital: comparisons among nursing home-acquired pneumonia NHAP, HCAP other than NHAP, and community-acquired pneumonia. Respirology. 2011;16:856–61.

26. Fujikura Y, Somekawa K, Manabe T. Aetiological agents of adult community-acquired pneumonia in Japan: systematic review and meta-analysis of published data. 2023;10:e001800.

27. Sweeney MT, Lubbers BV, Schwarz S, Watts JL. Applying definitions for multidrug resistance, extensive drug resistance and pandrug resistance to clinically significant livestock and companion animal bacterial pathogens. J Antimicrob Chemother. 2018;73(6):1460–3.

28. Giedraitienė A, Vitkauskiene A, Naginiene R, Pavilonis A. Antibiotic resistance mechanisms of clinically important bacteria. Medicina. 2011;47(3):19.

29. Jinghua M, Gaizhuang L, Qiaoli C. Pathogens and antibiotic resistance of children with community-acquired pneumonia. Biomedical Res. 2017;28:8839–43.

30. Adhanom G, Gebreegziabiher D, Weldu Y, Wasihun AG, Araya T, Legese H, et al. Species, risk factors, and Antimicrobial susceptibility profiles of bacterial isolates from HIV-Infected patients suspected to have Pneumonia in Mekelle Zone, Tigray. North Ethiopia. 2019;2019:8768439.

31. Yanagihara K, Matsumoto T, Aoki N, Sato J, Wakamura T, Kiyota H, et al. Nationwide surveillance of bacterial respiratory pathogens conducted by the Surveillance Committee of Japanese Society of Chemotherapy, the Japanese Association for Infectious Diseases, and the Japanese society for clinical microbiology in 2014: General view of the pathogens' antibacterial susceptibility. J Infect Chemother. 2019;25:657–68.

32. Leishker AH, Kolb GF. Aspiration pneumonia: management in Germany. Eur Geriatr Med. 2011;2:184–6.

33. Kohno S, Imamura Y, Shindo Y, Seki M, Ishida T, Teramoto S, et al. Clinical practice guidelines for nursing- and healthcare-associated pneumonia (NHCAP). Respir Investig. 2013;51:103–26.

34. Bartlett JG. How important are anaerobic bacteria in aspiration pneumonia: when should they be treated and what is optimal therapy. Infect Dis Clin. 2013;27:149–55.

35. DiBardino DM, Wunderink RG. Aspiration pneumonia: a review of modern trends. J Crit Care. 2015;30:40–8.

36. Asai N, Watanabe H, Shiota A, Kato H, Sakanashi D, Hagihara M, et al. Efficacy and accuracy of qSOFA and SOFA scores as prognostic tools for community-acquired and healthcare-associated pneumonia. Int J Infect Dis. 2019;84:89–96.

37. Chakra CNA, Pepin J, Sirard S, Valiquette L. Risk factors for recurrence, complications and mortality in Clostridium difficile infection: a systematic review. PLoS ONE. 2014;9:e107420.

38. Asai N, Sakanashi D, Suematsu H, Kato H, Shiota A, Hagihara M, et al. Observational study in a single institute in Japan: how many community-onset pneumonia patients would have Clostridioides difficile infections after treatment? J Infect Chemother. 2020;26:1104–6.

39. Asai N, Suematsu H, Ohashi W, Shibata Y, Sakanashi D, Kato H, et al. Ceftriaxone versus tazobactam/piperacillin and carbapenems in the treatment of aspiration pneumonia: a propensity score matching analysis. J Infect Chemother. 2021;27:1465–70.

40. Farahat F, Bukhari O, Basfar I, Alammari A, Zaatari A, Alsaedi A, et al. Clinical characteristics and outcomes of community-acquired pneumonia in western Saudi Arabia: a four-year retrospective analysis of medical records. J Infect Public Health. 2021;14:960–6.

41. Pichichero ME, Casey JR. Safe use of selected cephalosporins in penicillin-allergic patients: a meta-analysis. Otolaryngol Head Neck Surg. 2007;136:340–7.

42. Finegold SM. Aspiration pneumonia. Rev Infect Dis. 1991;13:S737–42.

43. Citron DM, Tyrrell KL, Merriam CV, Goldstein EJ. In Vitro activity of ceftaroline against 623 diverse strains of anaerobic bacteria. Antimicrob Agents Chemother. 2010;54:1627–32.

44. Kato H, Hagihara M, Asai N, Hirai J, Yamagishi Y, Iwamoto T, et al. Comparison between Ceftriaxone and Sulbactam-Ampicillin as initial treatment of community-acquired pneumonia: a systematic review and Meta-analysis. Antibiot (Basel). 2022;11:1291.

45. Fujita K, Takata I, Sugiyama H, Suematsu H, Yamagishi Y, Mikamo H. Antimicrobial susceptibilities of clinical isolates of the anaerobic bacteria which can cause aspiration pneumonia. Anaerobe. 2019;57:86–9.

46. Stoeckel K, McNamara PJ, Brandt R, Plozza-Nottebrock H, Ziegler WH. Effects of concentration-dependent plasma protein binding on ceftriaxone kinetics. Clin Pharm. 1981;29:650–7.

47. Rocephin. Ceftriaxone for Injection) [Prescribing information]; F. Hoffmann-La Roche. Basel, Switzerland: Ltd.; 2020.

48. Bishaw BM, Tegegne GT, Berha AB. Appropriate use of Ceftriaxone in Sub-saharan Africa: a systematic review. Infect Drug Resist. 2021;14:3477–84.

49. Heffernan AJ, Curran RA, Denny KJ, Sime FB, Stanford CL, McWhinney B, et al. Ceftriaxone dosing in patients admitted from the emergency department with sepsis. Eur J Clin Pharmacol. 2021;77:207–14.

50. David N, Henry F, Michael S, Andrew T, Helen W. The Sanford Guide to Antimicrobial Therapy 2021; Antimicrobial Therapy Inc.: Sperryville, VA, USA, 2021.

51. Kato H, Hagihara M, Morikawa Y, Asai N, Mikamo H, Iwamoto T. Retrospective comparison of the effectiveness and Safety of Ceftriaxone 1 g twice daily versus 2 g once Daily for treatment of Aspiration Pneumonia. Antibiot (Basel). 2022;11:983.

52. Kato H, Hagihara M, Hiramatsu SI, Suematsu H, Nishiyama N, Asai N, et al. Evaluating the antimicrobial efficacy of ceftriaxone regimens: 1 g twice daily versus 2 g once daily in a murine model of Streptococcus pneumoniae pneumonia. JAC Antimicrob Resist. 2024;6:dlae092.

53. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol. 2016;14(8):523–34.

54. Sirivongrangson P, Kulvichit W, Payungporn S, Pisitkun T, Chindamporn A, Peerapornratana S, et al. Endotoxemia and circulating bacteriome in severe COVID-19 patients. Intensiv Care Med Exp. 2020;8(1):1–15.

55. Robertson L, Caley JP, Moore J. Importance of Staphylococcus aureus in pneumonia in the 1957 epidemic of influenza A. Lancet. 1958;2:233–6.

56. Herzog H, Staub H, Richterich R. Gas-analytical studies in severe pneumonia; observations during the 1957 influenza epidemic. Lancet. 1959;1:593–7.

57. Morris DE, Cleary DW, Clarke SCJ. Secondary bacterial infections associated with influenza pandemics. Front Microbiol. 2017;8:1041.

58. Goldblatt D, Hussain M, Andrews N, Ashton L, Virta C, Melegaro A, et al. Antibody response to nasopharyngeal carriage of Streptococcus pneumoniae in adults. J Infect Dis. 2005;192:387–93.

59. Wu CP, Adhi F, Highland K. Recognition and management of respiratory co-infection and secondary bacterial pneumonia in patients with COVID-19. Cleve Clin J Med. 2020;87:659–63.

60. Vaughn VM, Gandhi TN, Petty LA, Patel PK, Prescott HC, Malani AN, et al. Empiric antibacterial therapy and community-onset bacterial coinfection in patients hospitalized with Coronavirus Disease 2019 (COVID-19): a multi-hospital cohort study. Clin Infect Dis. 2021;72(10):e533–41.

61. Iscanli I, Aydin M, Saylan B. Clinical characteristics and risk factors associated with secondary bacterial pneumonia among COVID-19 patients in ICU. J Infect Dev Ctries. 2023;17:1387–93.

62. Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. N Engl J Med. 2007;357(14):1373–81.

Publisher's Note