

Antibacterial treatment of aspiration pneumonia in older people: a systematic review

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Background: Aspiration pneumonia is a common problem in older people with high mortality and increasing prevalence.

Objective: The aims of this paper were to systematically review the literature on the antibacterial treatment of aspiration pneumonia in elderly patients and identify the microbiology of aspiration pneumonia.

Materials and methods: EMBASE, MEDLINE, and Cochrane databases were systematically searched for studies that examined the clinical efficacy of antibiotic treatment in elderly patients with aspiration pneumonia. Information on study design, antibiotic treatment, study population, participants, microbiology, clinical outcomes, adverse events, and mortality was recorded.

Results: There were no definitive clinical trials, placebo-controlled trials, or meta-analyses. Of the eight studies selected for inclusion in the review, the majority utilized and/or compared broad-spectrum antibiotics. No specific antibacterial agent had evidence of superior efficacy. Broad-spectrum antibiotics resulted in the emergence of multiresistant organisms. Anaerobic bacteria were infrequently isolated, suggesting a less important role in the pathogenesis of aspiration pneumonia.

Conclusion: There is limited evidence with regard to the use of antibiotics in older patients with aspiration pneumonia. Research providing an evidence base for the treatment of aspiration pneumonia in older people is required.

Keywords: aspiration pneumonia, antibiotics, antibacterial, antimicrobial, older people

Introduction

The incidence of aspiration pneumonia is difficult to determine, because there are few diagnostic markers for aspiration and most studies do not distinguish between aspiration pneumonia and aspiration pneumonitis.¹ Furthermore, studies suggested that as much as 5%–15% of people diagnosed with community-acquired pneumonia (CAP) actually have aspiration pneumonia,^{2,3} even more so in residential aged-care facility (RACF) residents.^{2,4} Aspiration pneumonia is becoming more common, with one study showing a 93.5% increase in annual hospitalizations for aspiration pneumonia between 1991 and 1998.⁵

The most common microorganisms isolated from aspiration pneumonia reflect those found in the oropharynx such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, and anaerobes.⁶ Gram-negative bacilli, *S. aureus*, and *Pseudomonas aeruginosa* are more common in institutionalized older people as a result of poor oral hygiene leading to dental decay and gingivitis.⁷ Pathogenic organisms are also seen in edentulous elderly patients suggesting that coating of the tongue by bacteria also contributes to the risk of aspiration pneumonia.⁸

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Aspiration pneumonia can lead to the development of necrotizing pneumonia or lung abscess, which may require a prolonged course of antibiotics and surgery.⁹ Aspiration pneumonia can be associated with high mortality with studies reporting figures between 0% and 85%.¹⁰ A study of 47 hospitalized patients reported that mortality was 90% if two or more lobes of the lung were involved and 41% if only one lobe was affected.¹¹ Aspiration pneumonia was an independent predictor of 30-day mortality after adjusting for pneumonia category, performance status, severity score, and treatment failure.¹²

Despite its high incidence and mortality, there has been a lack of research on the treatment of aspiration pneumonia. Hence, the aims of this systematic review were to describe the microbiology of aspiration pneumonia and to determine whether there are data to support optimal antibiotic management in elderly patients.

Materials and methods

Information sources

EMBASE (1980 to April 12, 2018), MEDLINE (1946 to April 14, 2018), and Cochrane (2005 to April 11, 2018) were searched on April 14, 2018, by two independent researchers (TB and JZ). Results were limited to studies in English involving human subjects. Reference lists of full-text papers were hand searched to identify any other relevant studies.

Search terms

Search terms were as follows: aspiration pneumon\$.m_titl. or pulmonary aspiration.m_titl. and treatment.mp. or management.mp. or pharmacotherapy.mp. or medication.mp. or antibiotics.mp. or antibacterial.mp. or antimicrobial.mp. Studies were also hand searched for additional relevant publications.

Eligibility criteria

Studies that examined the clinical effectiveness of antibiotic treatment for aspiration pneumonia were selected. All study designs except case reports were included. Studies were excluded if they reported only the treatment of necrotizing pneumonia and lung abscess without a clear history of preceding aspiration or did not include elderly patients (>65 years old). Any discrepancies regarding eligibility or other criteria were resolved by consensus between the two authors, TB and JZ.

Data items

Information on study design and antibiotic treatment including dose and route, study population, number and age of

participants, microbiology, clinical efficacy, and any other outcome measures, such as adverse reactions and mortality, was extracted from each study.

Risk of bias assessment

The Cochrane Risk of Bias Assessment Tool¹³ was used to assess the quality of all included studies.

Results

The database search generated 521 studies of which 354 were reviewed for eligibility after duplicates were removed. After the application of exclusion criteria, eight studies were included in the systematic review (Figure 1).

Microbiology

Table 1 summarizes the microbiological sampling techniques used and the organisms found in the eight studies.

Mier et al¹⁴ took protected brush specimens from 52 patients as well as urine and blood cultures. There were two positive blood cultures with one patient having *S. aureus* in both the blood culture and protected brush specimen. The other patient grew *S. pneumoniae* in their blood culture with a negative protected brush specimen. It should be noted that brush specimens were taken after the administration of antibiotics which might reduce the identification of anaerobes.

In the study by Marumo et al,¹⁵ anaerobic cultures were not undertaken on sputum specimens.¹⁵ This study identified specific pathogens in 55 patients (47%) using urinary antigen test, blood, sputum, or pleural effusion culture, with *S. pneumoniae* being the most frequently isolated organism identified in 26 patients (22.2%), followed by methicillin-sensitive *S. aureus* (MSSA; 10.3%) and *H. influenzae* (6%; Table 1).

Kadowaki et al¹⁶ only used sputum cultures and did not identify any anaerobic bacteria. Of the 100 patients, they obtained sputum samples from 99 patients. 42.4% of these cultures were negative. Gram-negative bacilli accounted for the majority of organisms (48.1%) and Gram-positive bacteria for 40.7% (Table 1). This study also examined the disappearance of these organisms from the sputum following antibiotic treatment and found that some bacteria remained detectable. Methicillin-resistant *S. aureus* (MRSA) emerged in patients who were administered all antibiotic regimens (22.7% in 3 g ampicillin/sulbactam, 25% in 6 g ampicillin/sulbactam, and 34.8% in panipenem/betamiprom [PAPM/BP]) except clindamycin.¹⁶

Ito et al¹⁷ utilized urinary antigen tests, serology, nasopharyngeal swabs, and blood and sputum culture and identified

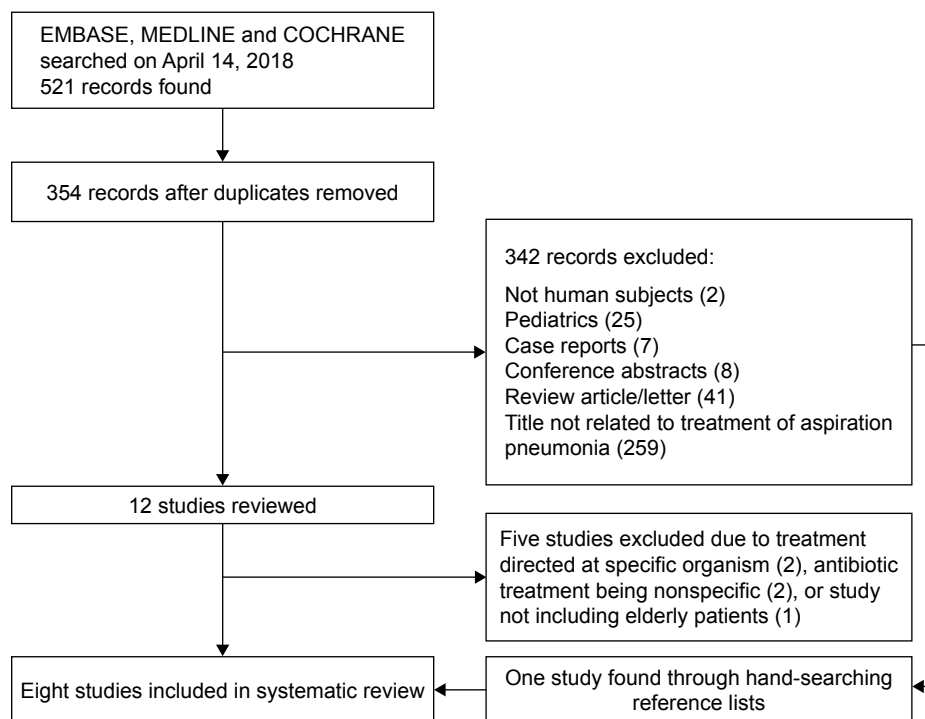


Figure 1 Flowchart of literature search.

a microbial diagnosis in 52% of patients. While Gram-positive bacteria, Gram-negative bacteria, and viruses were all isolated, no anaerobes were cultured. It is interesting to note that mixed infection with other bacteria and nonbacterial pathogens occurred in nine patients who were culture positive for *S. pneumoniae*.¹⁷

While the absence of anaerobes isolated on sputum culture is not surprising, the tracheal and blood cultures performed on all patients enrolled in the study by Talaie et al¹⁸ also failed to yield any anaerobic bacteria. Their results showed a positive blood culture in 18.6% of patients in the ceftriaxone/clindamycin treatment arm, with 4.3% of cultures positive for *S. aureus*. In the cefepime/clindamycin group, 17.1% of blood cultures were positive including 7.1% positive for *S. aureus*. Tracheal cultures were positive in 38.6% and 41.4% of these patients, respectively. A combination of *Klebsiella pneumoniae* and *Staphylococcus coagulase* was found in 12.9% and 14.3%, respectively.¹⁸

Tokuyasu et al¹⁹ used bronchoscopy to obtain aspirated sputum samples from the lower respiratory tract and isolated anaerobic organisms in 27.4% and Gram-negative rods in 51.6% of patients. The Gram-positive organisms isolated were *Streptococcus agalactiae*, MRSA, *S. pneumoniae*, MSSA, and *Streptococcus non AB*, and 54.8% of patients had mixed growth (Table 1).¹⁹

All 70 enrolled participants in the study by Allewelt et al²⁰ had microbiological sampling through either protected

specimen brush, bronchoalveolar lavage, sputum, transthoracic puncture, or bronchoscopically obtained bronchial secretions. Bacteria were identified in 58 patients, with mixed infection present in 32 of these patients. Anaerobes were found in 25 cases from protected specimen brush and bronchoalveolar lavage. The largest group of organisms isolated was Gram-positive bacteria, which accounted for 51 cases while Gram-negative bacteria were responsible for 42 cases (Table 1).²⁰

Ott et al²¹ used more invasive procedures to obtain microbiological samples including bronchoalveolar lavage, protected specimen brush, and transthoracic puncture. Of 139 patients, 70 patients had positive cultures. Multiple organisms were found in 24 of these patients. In patients with aspiration pneumonia, no anaerobes were cultured from their specimens. The aerobes consisted of 40.6% Gram-positive bacteria and 59.4% Gram-negative bacteria (Table 1). Patients with aspiration pneumonia with lung abscess grew both anaerobic and aerobic bacteria; however, the only anaerobes isolated were *Prevotella* spp. The Gram-positive bacteria were more frequent than Gram-negative bacteria (55.6% vs 33.4%). It is important to note that some patients were treated with antibiotics prior to enrollment in this study.²¹

All eight studies used different, and some multiple, sampling techniques to identify microorganisms. Invasive techniques, such as bronchoscopy, recovered more anaerobic

Table 1 Microbiology and sampling techniques used in the included studies

Study	Microbiological sampling techniques	Number of positive cultures	Microbiology		
			Anaerobes	Gram-positive	Gram-negative
Mier et al ¹⁴	Protected brush specimens, urine and blood cultures	19 (36.5%) positive protected brush specimens (single organism in 12 patients, multiple in 7 patients) Two positive blood cultures	<i>Peptostreptococcus</i> spp. (5), <i>Prevotella</i> spp. (1), <i>Prevotella</i> spp. (2), <i>P. intermedia</i> (2), <i>P. buccae</i> (2), <i>P. melaninogenica</i> (3) <i>Bacteroides</i> spp. (2) and <i>F. nucleatum</i> (1), others (7)	<i>S. aureus</i> (6 patients), <i>S. pneumoniae</i> (4 patients), <i>S. viridians</i> (1)	<i>P. aeruginosa</i> (3 patients), <i>P. mirabilis</i> (2 patients), <i>H. influenzae</i> (2 patients), <i>E. coli</i> (2 patients), <i>S. marcescens</i> (1), <i>E. cloacae</i> (1), <i>M. morgani</i> (1), and <i>K. pneumoniae</i> (1)
Allewelt et al ²⁰	Protected specimen brush, bronchoalveolar lavage, bronchoscopy, transthoracic puncture and sputum	Two positive blood cultures 118 pathogens were identified in 58 (82.6%) patients with 26 having a single organism and 32 patients showing mixed infection		<i>S. aureus</i> (14), <i>Streptococcus</i> spp. (17), <i>S. pneumoniae</i> (6), <i>S. milleri</i> (2), others (12)	<i>E. coli</i> (5), <i>Proteus</i> spp. (5), <i>K. pneumoniae</i> (2), <i>K. oxytoca</i> (3), <i>H. influenzae</i> (2), <i>Haemophilus</i> spp. (2), <i>H. parainfluenzae</i> (3), <i>Pseudomonas</i> spp. (3), <i>P. aeruginosa</i> (3), <i>Enterobacter</i> spp. (3), <i>Acinetobacter</i> spp. (2), <i>P. multocida</i> (1), <i>Neisseria</i> spp. (3), <i>S. maltophilia</i> (1), and others (4)
Kadowaki et al ¹⁶	Sputum cultures	57.6% of cultures were positive from a total of 99 patients		MRSA (12.3%), MSSA (9.8%), and <i>S. pneumoniae</i> (4.9%)	<i>K. pneumoniae</i> (2.4%), <i>E. coli</i> (4.9%), <i>E. cloacae</i> (4.9%), <i>P. aeruginosa</i> (4.9%), and <i>H. influenzae</i> (3.7%)
Ott et al ²¹	Bronchoalveolar lavage, protected specimen brush, transthoracic puncture, or sputum culture	102 pathogens identified in 70 (50.4%) patients (46 patients having single organism, 24 patients showing mixed infection)	AP: no anaerobes cultured AP with abscess: 11.1% anaerobes: <i>Prevotella</i> spp. (1) PLA: 29.6% anaerobes: <i>Fusobacterium</i> spp. (2), <i>B. fragilis</i> (1), <i>F. nucleatum</i> (1), <i>P. intermedia</i> (1), <i>P. denticola</i> (1), <i>P. oralis</i> (1)	AP: 40.6% Gram-positive bacteria composed of <i>S. aureus</i> (15), <i>Streptococcus</i> spp. (5), <i>S. pneumoniae</i> (1) AP with abscess: 55.6% Gram-positive bacteria (<i>S. pneumoniae</i> [2], <i>S. aureus</i> [1], and <i>Streptococcus</i> spp. [1], <i>S. milleri</i> [1]) PLA: 37% Gram-positive bacteria composed of <i>S. aureus</i> (4) and <i>Streptococcus</i> spp. (2), <i>S. pneumoniae</i> (1), <i>S. milleri</i> (1)	AP: 59.4% Gram-negative: <i>E. coli</i> (7), <i>K. pneumoniae</i> (7), <i>P. aeruginosa</i> (7), <i>P. mirabilis</i> (3), <i>K. oxytoca</i> (2), <i>H. influenzae</i> (2), <i>H. parainfluenzae</i> (2), <i>Enterobacter</i> spp. (2), <i>S. marcescens</i> (2), <i>C. freundii</i> (1), <i>M. catarrhalis</i> (1), <i>M. morgani</i> (1). AP with abscess: 33.4% Gram-negative bacteria: <i>E. coli</i> (1), <i>K. pneumoniae</i> (1), <i>H. influenzae</i> (1). PLA: 33.4% Gram-negative bacteria: <i>K. pneumoniae</i> (2), <i>H. influenzae</i> (2), <i>E. coli</i> (1), <i>P. aeruginosa</i> (1), <i>C. freundii</i> (1), <i>P. mirabilis</i> (1), <i>S. marcescens</i> (1) <i>K. pneumoniae</i> was found in 13.6% of tracheal cultures
Talae et al ¹⁸	Blood cultures and tracheal cultures	Blood cultures were positive in 17.9% of patients 40% of patients had positive tracheal cultures		<i>S. aureus</i> was detected in 5.71% of blood cultures. <i>Staphylococcus</i> coagulase was found in 13.6% of tracheal cultures	
Tokuyasu et al ¹⁹	Blood cultures and aspirated sputum samples from the lower respiratory tract using bronchoscopy	111 organisms grown in sputum culture from 54 (87.1%) patients (20 patients with single organism, 34 patients with mixed organisms). Blood cultures were only positive for contaminants	<i>Fusobacterium</i> spp. (3), <i>S. milleri</i> (2), <i>Peptococcus</i> spp. (2), <i>B. fragilis</i> (1)	<i>S. agalactiae</i> (19), MRSA (15), <i>S. pneumoniae</i> (7), MSSA (4), <i>Streptococcus</i> non-AB (1)	<i>K. pneumoniae</i> (11), <i>P. aeruginosa</i> (10), <i>E. coli</i> (7), <i>H. influenzae</i> (6), <i>Enterococcus</i> (2), <i>M. catarrhalis</i> (1), <i>H. parainfluenzae</i> (1), <i>H. parahaemolyticus</i> (1), <i>E. cloacae</i> (1), <i>E. aerogenes</i> (1), <i>E. gergoviae</i> (1), <i>Proteus</i> spp. (1)

Ito et al ¹⁷	Urinary antigen tests, serology, nasopharyngeal swabs, blood culture and sputum culture	Microbiological diagnosis was achieved in 52% of patients	S. pneumoniae (25.8%), MSSA (1.84%), MRSA (3.07%)	K. pneumoniae (3.68%), E. coli (3.68%), H. influenzae (1.23%), P. aeruginosa (1.84%), M. catarrhalis (0.61%), L. pneumophila (1.23%), C. pneumoniae (2.45%) H. influenzae (6%), E. coli (1.7%), P. aeruginosa (1.7%)
Marumo et al ¹⁵	Urinary antigen tests, blood culture, sputum culture or pleural effusion culture	47% of patients had positive cultures	S. pneumoniae (22.2%), MSSA (10.3%), MRSA (0.9%)	K. pneumoniae (3.68%), E. coli (3.68%), H. influenzae (1.23%), P. aeruginosa (1.84%), M. catarrhalis (0.61%), L. pneumophila (1.23%), C. pneumoniae (2.45%) H. influenzae (6%), E. coli (1.7%), P. aeruginosa (1.7%)
<p>Abbreviations: AP, aspiration pneumonia; B. fragilis, Bacteroides fragilis; C. freundii, Citrobacter freundii; C. pneumoniae, Chlamydia pneumoniae; E. aerogenes, Enterobacter aerogenes; E. cloacae, Enterobacter cloacae; E. coli, Escherichia coli; E. gergoviae, Enterobacter gergoviae; F. nucleatum, Fusobacterium nucleatum; H. influenzae, Haemophilus influenzae; H. parainfluenzae, Haemophilus parainfluenzae; K. oxytoca, Klebsiella oxytoca; K. pneumoniae, Klebsiella pneumoniae; L. pneumophila, Legionella pneumophila; M. catarrhalis, Moraxella catarrhalis; M. morgani, Morganella morgani; MRSA, methicillin-resistant S. aureus; MSSA, methicillin-sensitive S. aureus; P. aeruginosa, Pseudomonas aeruginosa; P. buccae, Prevotella buccae; P. denticola, Prevotella denticola; P. intermedia, Prevotella intermedia; PLA, primary lung abscess; P. melaninogenica, Prevotella melaninogenica; P. mirabilis, Proteus mirabilis; P. multocida, Pasteurella multocida; P. oralis, Prevotella oralis; S. aureus, Staphylococcus aureus; S. maltophilia, Stenotrophomonas maltophilia; S. marcescens, Serratia marcescens; S. milleri, Streptococcus milleri; S. pneumoniae, Streptococcus pneumoniae; spp., species; S. viridians, Streptococcus viridians.</p>				

bacteria than less invasive techniques, such as sputum and blood cultures which isolated mainly aerobic bacteria. The most common Gram-negative organisms were *Escherichia coli*, *K. pneumoniae*, and *P. aeruginosa*, and the most common Gram-positive organisms were *S. aureus* and *S. pneumoniae*. Many studies reported mixed growth. The results are limited by the poor sensitivity and specificity of respiratory isolates²² and the prior administration of antibiotics in some studies.

Antibacterial treatment of aspiration pneumonia

Study characteristics are summarized in Table 2. Studies identified participants for inclusion in the studies based on both clinical and radiological evidence of aspiration pneumonia. The eight studies included are of reasonable quality, and the majority have used comparative and prospective design protocols.

Mier et al¹⁴ examined the use of penicillin G as an initial antibiotic treatment in patients admitted to the intensive care unit (ICU), with treatment amended if the organism was resistant to penicillin. The patients were thus divided into two groups; with group one receiving penicillin and group 2 receiving tailored antibiotic therapy, although antibiotic class and regimen was not specified. There were significant differences in patient characteristics between the groups: those from group 2 were older, more unwell (lower blood pressure, higher creatinine), and admitted from another hospital ward rather than the community. Patients in group 2 spent longer time in ICU (6.7±4.7 vs 11.2±8.8 days, $P \leq 0.02$) and on mechanical ventilation (3.5±2.7 vs 6.1±4.6 days, $P = < 0.03$), but there was no significant difference in mortality.

Allewelt et al²⁰ randomized patients with aspiration pneumonia and primary lung abscess into treatment with either ampicillin/sulbactam or clindamycin ± cephalosporin, with 72.7% of the clindamycin group receiving a cephalosporin. Cephalosporins included cefotiam (n=12), cefuroxime (n=6), cefazolin (n=2), ceftazidime (n=2), cefotaxime (n=1), and ceftriaxone (n=1). Twenty-five subjects were excluded from the final analysis because of the violation of exclusion criteria, receiving antibiotics not in the treatment protocol or loss to follow-up. The final two groups were similar in baseline characteristics, with the only significant difference being a greater majority of males in the ampicillin/sulbactam group (86.5% vs 63.6%, $P = 0.05$). The study found that, in patients treated with ampicillin/sulbactam, improvement occurred in 73% of patients at the end of therapy and in 67.5% by the final examination. In 66.7% of patients treated with clindamycin, there was an improvement at the end of

Table 2 Study characteristics

Study	Intervention	Study design	Study population	Number of participants	Age (years)	Clinical efficacy	Other outcomes	Limitations
Mier et al ⁴	Penicillin G (group 1; n=35) vs various unspecified antibiotics targeting specific penicillin-resistant organisms (group 2; n=17)	Observational prospective study	Patients admitted to ICU with clinical and radiological evidence of AP	52	Mean age =48.8±21.4	Days in ICU: group 1: 6.7 days ± 4.7 vs group 2 11.2±8.8 (P<0.02) Days on mechanical ventilation: group 1: 3.5±2.7 vs group 2 6.1±4.6 (P<0.03)	Mortality rate was equal in both groups. 3 patients died in each group, not specifically due to infection	Crossover of groups, eg. antibiotics in group 1 were changed from penicillin to another antibiotic. Various antibiotics were used in group 2, and they were not listed. Different group numbers
Allewelt et al ²⁰	ABPC/STB (n=37) vs clindamycin ± cephalosporin (n=33)	Open, randomized, comparative, and prospective multicenter study	Patients hospitalized with clinical or radiographic evidence of AP or PLA	95 (25 excluded)	17–90	ABPC/STB vs clindamycin ± cephalosporin: clinical response =73% vs 66.7% at the end of the therapy 67.5% vs 63.5% at days 7–14. One-sided Farrington–Manning test showed a marginal advantage for ABPC/STB at 10% equivalence range, but not 15% Mean duration =22.7 vs 24.1 days	Mortality rate was 12.9% with 7 patients dying in the clindamycin group and 2 from the ABPC/STB Treatment failure with premature discontinuation occurred in 19.5% of ABPC/STB vs 24.4% in the clindamycin group	Did not distinguish CAP from HAP Not blinded
Kadowaki et al ⁶	IV ABPC/STB (1.5 g; n=25) vs IV ABPC/STB (3 g) (n=25) vs IV clindamycin (n=25) vs IV PAPM/BP (n=25) vs MXF (n=71) vs ABPC/STB (n=68)	Randomized prospective study	Patients hospitalized in Japan with mild–moderate AP	100	71–94	Clinical efficacy after 8–10 days of treatment: ABPC/STB 3 g =84%, ABPC/STB 1.5 g =76%, clindamycin =76%, PAPM/BP =88% (P=0.6249)	No significant difference in adverse events (P=0.9717) Incidence of MRSA post treatment was significantly lower in the clindamycin group (P=0.0255)	No blinding Antibiotic changed if deemed to be ineffective
Ott et al ¹¹	MXF (n=71) vs ABPC/STB (n=68)	Prospective, randomized, open-label, multicenter study	Patients with clinical and radiological features of either AP or lung abscess recruited from 15 inpatient centers in Germany	139	Mean age in the MXF group =59.5±16.8 Mean age in the ABPC/STB group =61.3±14.5	Clinical success rates: MXF vs ABPC/STB AP =51% vs 53% PLA =56% vs 67% AP with abscess =50% vs 57% Mean duration of treatment: MXF vs ABPC/STB (P>0.05)	Mortality: a total of 20 patients died (14.4%) with 6 in the MXF group and 14 from the ABPC/STB group Adverse effects: 54.9% in the MXF group and 54.4% in the ABPC/STB group (eg. gastrointestinal disorders, cardiac problems, and raised liver enzymes).	Patients treated with previous antibiotics prior to enrollment No blinding of subjects or investigators

Talaie et al ¹⁸	Cefepime/clindamycin (n=70) vs ceftriaxone/clindamycin (n=70)	Open, randomized, prospective study	ICU patients admitted post poisoning with clinical and radiological signs of AP	140	13-95	AP =13.1±7.7 vs 11±6 days PLA =48.4±40.6 vs 40.2±27.4 days AP with abscess =43.3±31.8 vs 46.5±45.1 days	21 patients in each group experienced serious side effects with 16.9% of patients in the MXF group and 13.2% in the ABPC/SBT group discontinuing treatment prematurely due to adverse effects	Random allocation, but not blinded
Tokuyasu et al ¹⁹	Meropenem	Prospective study	Hospitalized patients with clinical and radiological signs of AP	62	Mean age =86.6±6.7	Improvement/cure rate: Day 5 – ceftriaxone (90%) vs cefepime (88.6%), P=0.79 Day 14 – ceftriaxone (93.8%) vs cefepime (90.9%), P=0.58 The clinical efficacy of meropenem treatment was found to be 61.3%. Duration of treatment was 8.7±2.6 days	Mortality rate: Days 5 and 14 – ceftriaxone (8.6%) vs cefepime (7.1%), P=0.75 No reported adverse events in either of the group Mortality rate was 6.7%. 5 patients died from pneumonia, and 1 patient died from respiratory failure. Adverse side effects were as follows: liver disorder (17.7%), diarrhea (8.1%), raised ALP (4.8%), and eosinophilia (14.5%)	No control/comparison group
Ito et al ¹⁷	TAZ/PIPC (n=81) vs IPM/CS (n=82)	Open-label, randomized, prospective study	Hospitalized patients with radiological and clinical signs of pneumonia and ≥1 condition placing them at risk of aspiration	163	Mean age =85±7	At the end of treatment, the clinical efficacy of TAZ/PIPC was 83% vs 82% for IPM/CS (P=0.92). Duration of treatment was 10.6±4.2 days for TAZ/PIPC vs 11.1±4.6 days for IPM/CS	Adverse events occurred in 31.6% of patients receiving TAZ/PIPC and 37.5% of patients on IPM/CS, with diarrhea and deranged LFTs being the most common side effects. <i>C. difficile</i> was isolated in 4 patients (3 receiving IPM/CS), Mortality rate within 30 days of admission was 15% in the TAZ/PIPC group and 24% in the IPM/CS group (P=0.12)	Selection criteria may have resulted in patients with CAP being enrolled in the study
Marumo et al ¹⁵	IV ABPC/SBT (ABPC/SBT) (n=81) vs IV AZM (n=36)	Prospective, observational, nonrandomized cohort study	Hospitalized patients with radiological and clinical signs of AP	117	69-87	Success rate of first-line antibiotics: ABPC/SBT 74.1% vs AZM 75% (P=1.0) Hospital days: ABPC/SBT 22.3 vs AZM 20.5 (P=0.654)	Mortality: ABPC/SBT 11.1% vs AZM 8.3% (P=0.753) Total antibiotic costs ABPC/SBT 2.94 vs AZM 2.19 (P=0.034)	Nonrandomized Anaerobic culture was not performed

Abbreviations: ABPC/SBT, ampicillin/sulbactam; AP, aspiration pneumonia; AZM, azithromycin; CAP, community-acquired pneumonia; *C. difficile*, *Clostridium difficile*; HAP, hospital-acquired pneumonia; ICU, intensive care unit; IPM/CS, imipenem/cilastatin; IV, intravenous; LFT, liver function test; MRSA, methicillin-resistant *S. aureus*; MXF, moxifloxacin; PAPM/BP, panipenem/betamiprom; PLA, primary lung abscess; *S. aureus*, *Staphylococcus aureus*; TAZ/PIPC, tazobactam/piperacillin.

therapy and 63.6% had improved by the final examination. Statistical analysis with a one-sided Farrington–Manning test showed an advantage for ampicillin/sulbactam over clindamycin at the 10% equivalence range, but the antibiotics were equally effective at the 15% equivalence range. However, treatment failure and a higher discontinuation rate were seen in the ampicillin/sulbactam group (24.4% vs 19.5%), while the 12.9% mortality rate was composed mainly of patients in the clindamycin group, perhaps suggesting that patients in the clindamycin group had more severe disease. The limitations of this study were the absence of blinding and administration of antibiotics prior to study inclusion, thus selecting for more resistant organisms. The authors concluded that this study suggests a possible, albeit very weak, advantage of ampicillin/sulbactam over clindamycin.

Kadowaki et al¹⁶ examined the use of ampicillin/sulbactam and clindamycin in patients with aspiration pneumonia aged between 71 and 94 years. This unblinded study compared three different antibiotics and different doses of ampicillin/sulbactam that were adjusted according to response. The study found no significant difference in the clinical efficacy, side effects, or treatment duration (Table 2) between the four groups. Patients on the full dose of ampicillin/sulbactam were noted to suffer from more diarrhea and blood-stained bowel discharge compared to patients receiving the half dose. The study was terminated early because MRSA emerged in all treatment groups, except clindamycin. Therefore, this study showed no difference in antibiotic efficacy with the major difference being adverse effect profiles.

Ott et al²¹ compared ampicillin/sulbactam to moxifloxacin in patients with aspiration pneumonia, primary lung abscess, and aspiration pneumonia with cavitation. The two groups were comparable in characteristics and dropout rate (32.4% vs 29.4%), and there was similar efficacy between the groups (moxifloxacin 52% vs ampicillin/sulbactam 57%). The incidence of treatment side effects was equivalent (moxifloxacin 54.9% vs ampicillin/sulbactam 54.4%). Treatment failure resulting in premature discontinuation occurred in 22.1% in the ampicillin/sulbactam group compared to 15.5% of the moxifloxacin group. The mortality rate was 14.4%, being composed of 14 patients from the ampicillin/sulbactam group and six patients from the moxifloxacin group. The main limitations were the absence of blinding and the inclusion of patients who had received antibiotics prior to recruitment.

Marumo et al¹⁵ compared ampicillin/sulbactam to azithromycin in patients admitted to hospital from an RACF or long-term care hospital with aspiration pneumonia.

This study showed that there was no difference in the success rate of first-line antibiotics between the ampicillin/sulbactam and azithromycin groups (74.1% vs 75%). There was no significant difference in mortality (11.1% vs 8.3%) or length of hospital stay (22.3 ± 7.3 vs 20.5 ± 8.1 days), although the length of stay was protracted. The participants were not randomized in this study, but patient characteristics were similar between groups, including the severity of pneumonia.

Ito et al¹⁷ evaluated the use of tazobactam/piperacillin and imipenem/cilastatin in the treatment of moderate-to-severe pneumonia in patients with at least one risk factor for aspiration pneumonia. Patients were recruited from the community or RACF. Baseline characteristics of the groups were not significantly different. At the end of treatment, resolution of pneumonia for tazobactam/piperacillin was 80% vs 79% (not significant) for imipenem/cilastatin in the modified intention-to-treat population and 83% vs 82% (ns) in those who adhered to the study protocol. However, the tazobactam/piperacillin group showed more prompt improvement with lower white cell count and temperature at day 4. In post hoc subgroup analyses, when antibiotics were analyzed against microbiological data, tazobactam/piperacillin was better at improving outcomes in patients with Gram-positive bacteria with and without mixed infection (96% vs 73%, $P=0.03$). There was no significant difference in adverse events (24 vs 32 events), with diarrhea being the most frequent adverse event in both groups. *Clostridium difficile* was isolated in four cases, with three cases in patients on imipenem/cilastatin. The mortality rate was 15% in the tazobactam/piperacillin group compared to 24% on imipenem/cilastatin, which was not statistically significant. The main limitation of this study was the fact that patients without aspiration pneumonia may have been enrolled due to the inclusion criteria stipulating that patients only had to have one risk factor for aspiration pneumonia. Some patients had positive viral cultures which was not consistent with bacterial aspiration pneumonia. Patients were not blinded to their treatment.

Tokuyasu et al¹⁹ examined the use of carbapenems for the treatment of aspiration pneumonia in patients ≥ 75 years old in a small prospective study. Participants had an average age of 86.6 years, 56% were from an RACF, 93.5% were bedbound, 50% were being fed with enteral feeding tubes, and 77.4% had at least one comorbidity. The duration of treatment with meropenem was 8.7 ± 2.6 days, and the main adverse side effects experienced were mild and included liver dysfunction, diarrhea, and eosinophilia. The efficacy rate was 61.3% with a mortality rate of 9.7% directly related to the aspiration pneumonia. Efficacy of treatment was lower in

patients with percutaneous endoscopic gastrostomy (PEG) feeding (44.8%) compared to the non-PEG group (75.8%; $P \leq 0.05$). This reflects patients with PEG tubes having a more severe pneumonia (89.7% vs 69.7%, $P=0.05$), as classified by the Japanese Respiratory Society (JRS) classification. There was no comparison or control group. There was a high rate of adverse events, and 33 (53%) patients grew new MRSA infections after receiving meropenem.

Talaie et al¹⁸ studied cefepime/clindamycin vs ceftriaxone/clindamycin in overdose patients with the evidence of aspiration pneumonia admitted to ICU with the majority requiring mechanical ventilation. The average age of patients in this study was approximately 32 years, but it included patients up to the age of 95 years and hence was included in this systematic review. The clinical response between the cefepime and ceftriaxone groups was not statistically significant at day 5 (88.6% vs 90%, $P=0.79$) or day 14 (90.9% vs 93.8%, $P=0.58$). No patients experienced any adverse reactions. The mortality rate was not statistically significant between the groups with 7.1% in the cefepime group and 8.6% in the ceftriaxone group ($P=0.75$). The high success rate seen in this study compared to previous studies is likely due to the young average age and the possible inclusion of patients with aspiration pneumonitis that may have improved without antibiotic treatment. Furthermore, the investigators were not blinded to the treatment groups. Extrapolation of these data to the older population is therefore problematic.

In summary, the antibiotics studied have predominantly been broad spectrum, covering both Gram-positive and Gram-negative bacteria, with the exception of penicillin and clindamycin that have relatively poor Gram-negative activity.²³ Inclusion of anaerobic cover was not universal, with only the following antibiotics having anti-anaerobic activity: clindamycin, moxifloxacin, carbapenems, and ampicillin/sulbactam.²³ Hence, these antibiotics covered the majority of the pathogens isolated through microbiological sampling, and similar efficacy rates were seen in all comparative trials. The most significant differences arose in side effect profiles and the development of resistant organisms. Studies were limited by the absence of blinding, lack of randomization, and participants receiving antibiotic treatment prior to enrollment.

Risk of bias within studies

All eight studies were assessed for the risk of bias using the Cochrane Risk of Bias Tool (Table S1). Performance and detection bias were found to be high in most studies due to the absence of blinding. Only three studies described

randomization of subjects.^{16,18,21} High attrition bias was suspected in the study by Allewelt et al²⁰ which analyzed outcomes of the “according-to-protocol” group with missing data from the “intention-to-treat” group due to participants either dropping out or being excluded from the study due to protocol violations. The absence of data on clinical efficacy,¹⁴ bacteriological response,²¹ and adverse events¹⁵ in three studies was suggestive of selective outcome reporting.

Discussion

There was a predominance of both Gram-negative and Gram-positive bacteria, while anaerobes were infrequently identified. This may reflect methodological issues related to the collection of samples, the use of anaerobic culture techniques, or prior administration of antibiotics. However, the consistency between the studies does seem to suggest that anaerobes are an infrequent cause of aspiration pneumonia. Negative cultures and results showing mixed growth were frequent.

To date, there have been no large, double-blinded, randomized control trials comparing different antibiotics commonly used to treat aspiration pneumonia. The majority of studies have been prospective in nature with randomization of groups, but minimal blinding and relatively small numbers of patients. They have utilized broad-spectrum antibiotics to cover Gram-positive, Gram-negative, and at times, anaerobic bacteria. For example, Talaie et al¹⁸ compared two groups of broad-spectrum cephalosporins. Both groups received clindamycin as well and the response rates in these groups (90.9% vs 93.8%) were higher compared to the study by Allewelt et al,²⁰ which used mainly moderate-spectrum cephalosporins. Carbapenems were the broadest spectrum antibiotics studied, but the study by Tokuyasu et al¹⁹ showed a very low clinical efficacy of 61.3%, especially when compared to the efficacy of 88% achieved with PAMP/BP in the study by Kadowaki et al¹⁶ and 82% in the study by Ito et al.¹⁷ This is likely due to the population studied, which included patients ≥ 75 years old with the majority being from RACFs with poor functional status, some receiving enteral feeding and many having multiple comorbidities. Nevertheless, the mortality rate was 9.7%,¹⁹ which is comparable with other studies.^{20,21} However, the most worrying and not unexpected result in these studies was the emergence of resistant organisms^{16,19} and *C. difficile*.¹⁷

The other five studies examined the clinical efficacy of penicillin with no significant difference found between the comparison groups. Four studies examined beta-lactam/beta-lactam inhibitors, but only one paper examined the

use of narrow-spectrum penicillin G in the treatment of aspiration pneumonia. Unfortunately, this study by Mier et al¹⁴ was flawed as all patients received an initial dose of penicillin G and then their antibiotic was changed depending on the culture results. Another study that examined the use of penicillin G was unable to be included in this literature review as the age range of the participants was not specified and only an average range of 50–55 years was given.²⁴ The study by Bartlett and Gorbach²⁴ showed a comparable efficacy of penicillin G (75%) to clindamycin (84%) in patients with aspiration pneumonia and primary lung abscess.

Therapeutic guidelines in Australia support first-line treatment with penicillin, clindamycin, or cephalosporins depending on severity, with piperacillin/tazobactam used as the second-line treatment if resistant Gram-negative organisms are thought to be present.²⁵ Metronidazole is added to the treatment regimen if there is evidence of anaerobic organisms,²⁵ despite the lack of evidence to support this recommendation.²⁶ While metronidazole has good in vitro activity against anaerobes, clinically it does not appear to be useful in anaerobic pulmonary infections.^{27,28}

The JRS, British Thoracic Society, and American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines recommend initial treatment with ampicillin/sulbactam,^{6,29,30} which is supported by four of the studies.^{15,16,20,21} ATS/IDSA also supports the use of clindamycin and carbapenam,³⁰ in which Kadowaki et al¹⁶ showed to be as efficacious as ampicillin/sulbactam.

The duration of antibacterial treatment and clinical outcomes in these studies may have been affected by other factors such as length of time patients remained *nil per os* (NPO), as Maeda et al³¹ showed that patients who were NPO for shorter periods had better nutritional status, shorter antibiotic duration, and less impaired swallowing ability. While this was not evident in Tokuyasu et al¹⁹ who demonstrated longer fasting periods in the non-PEG group, but no significant difference in the nutritional status or antibiotic duration between the groups, this could be due to the PEG group having greater pneumonia severity. Only two other studies commented on the introduction of oral intake, but no specific timeframes were given.^{15,16} Introduction of oral intake by Marumo et al¹⁵ was based on the decision of the physician, which is known to be highly variable and usually longer than necessary.³² However, patients in the study by Kadowaki et al¹⁶ were permitted oral intake only after a period of swallowing rehabilitation and comprehensive oral care, two strategies known to prevent relapse of aspiration pneumonia.³³ The fact that only one study implemented

preventative measures is in keeping with current data demonstrating that recurrence prevention of aspiration pneumonia by physicians is poor.³⁴

This is the only systematic review that has analyzed the antibacterial treatment of aspiration pneumonia in the older person. However, it is limited by including studies only in English. The lack of randomized control trials and the heterogeneity between the eight studies meant that a meta-analysis could not be performed. This study examined only the treatment of aspiration pneumonia and not prevention, which is an important consideration given that aspiration pneumonia is usually a recurrent problem.^{33,34} Randomized controlled trials need to be performed now, so that a more evidence-based treatment algorithm can be designed. For example, it would be beneficial to compare intravenously (IV) to orally administered ampicillin/sulbactam and penicillin G to ampicillin/sulbactam.

Conclusion

This literature review highlights the paucity of data guiding the treatment of aspiration pneumonia. Given the rapidly aging population and the high incidence and mortality associated with aspiration pneumonia, more research needs to be directed toward both prevention and treatment. Existing evidence supports the use of broad-spectrum antibiotics, but consideration needs to be given to the rapidly emerging problem of antibacterial resistance juxtaposed with the slow development of new antibacterial agents, calling for judicious, evidence-based prescribing. Research now needs to be directed toward comparing these agents to more narrow-spectrum antibiotics to determine whether there is a difference in therapeutic outcomes.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Risk of bias within included studies

Study	Selection bias		Performance bias		Detection bias	Attrition bias	Reporting bias
	Sequence generation	Allocation concealment	Blinding participants	Blinding personnel	Blinding outcome	Incomplete outcome data	Selective outcome reporting
Mier et al ¹	High	High	High	High	High	Days in ICU – low Days on mechanical ventilation – low Mortality – low	High
Allewelt et al ²	Unclear	Unclear	High	High	High	Clinical efficacy – high Bacteriological response – high Adverse events – high Mortality – high	Low
Kadowaki et al ³	Low	Low	High	High	High	Clinical efficacy – low Bacteriological response – low Adverse events – low Economic analysis – low New appearance of MRSA – low Mortality – low	Low
Ott et al ⁴	Low	Low	High	High	High	Clinical efficacy – low Adverse events – low Mortality – low	High
Talaie et al ⁵	Low	Low	High	High	High	Clinical efficacy – low Adverse events – low Mortality – low	Low
Tokuyasu et al ⁶	High	High	High	High	High	Clinical efficacy – low Adverse events – low Mortality – low	Low
Ito et al ⁷	Unclear	Unclear	High	High	Low	Clinical efficacy – low Adverse events – low Mortality – low	Low
Marumo et al ⁸	High	High	High	High	High	Clinical efficacy – low Length of stay – low Economic analysis – low Mortality – low	High

Abbreviations: ICU, intensive care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.

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