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Review

Ceftaroline fosamil as a potential treatment option for *Staphylococcus aureus* community-acquired pneumonia in adults

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ABSTRACT

Staphylococcus aureus (*S. aureus*), including methicillin-resistant *S. aureus* (MRSA), is an important aetiological cause of community-acquired pneumonia (CAP) and associated with significant morbidity and mortality. Empiric therapy for CAP frequently consists of β-lactam monotherapy or β-lactam/macrolide combination therapy. However, such agents are often ineffective against *S. aureus* and do not reflect the emergence and increasing prevalence of MRSA in the community setting. Ceftaroline fosamil is a fifth-generation parenteral cephalosporin with broad-spectrum activity against Gram-positive pathogens – such as *S. aureus* (including MRSA), *Streptococcus pneumoniae* and *Streptococcus pyogenes* – and typical Gram-negative pathogens, including *Haemophilus influenzae* and *Moraxella catarrhalis*. The approval of ceftaroline fosamil in the United States and Europe for the treatment of adults with moderate-to-severe CAP was based on two phase 3 trials (FOCUS 1 and 2), which demonstrated that ceftaroline fosamil was non-inferior to ceftriaxone, a standard empiric treatment for CAP, while exhibiting a comparable safety profile. Although head-to-head trials of ceftaroline fosamil versus comparators against MRSA CAP are lacking, the effectiveness of ceftaroline fosamil in subpopulations of patients not covered by phase 3 trials (e.g. those with MRSA CAP or severe renal impairment) has been demonstrated in the Clinical Assessment Program and Teflaro Utilization Registry (CAPTURE) study. As ineffective empiric therapy is associated with adverse outcomes, including mortality and increased costs, ceftaroline fosamil, with its extended spectrum of activity, is an attractive alternative to standard antibiotic CAP regimens.

1. Introduction

Community-acquired pneumonia (CAP) is an acute infection of the pulmonary parenchyma, accompanied by the presence of clinical features and new pulmonary infiltrates on chest radiography, in individuals who have not been recently hospitalised or had regular exposure to the healthcare system [1,2]. Despite advances in antimicrobial therapies, CAP remains a significant cause of morbidity and mortality worldwide [3]. During the past decade, *Staphylococcus aureus* (*S. aureus*), including methicillin-resistant *S. aureus* (MRSA), has emerged as a cause of severe CAP, with an increased risk of mortality relative to all-cause non-*S. aureus* CAP [4]. Adverse outcomes associated with pathogenic strains of *S. aureus* can be attributed to its rapid adaptive ability to develop antibiotic resistance (e.g. MRSA) and its expression of structural and secretory virulence determinants that facilitate colonisation, dissemination into host tissues and evasion of the immune system [5,6]. MRSA CAP classically presents as rapidly progressive severe respiratory disease in previously healthy young individuals [7]. The aggressive nature of some MRSA strains, due to extracellular cytotoxin production (e.g. Panton–Valentine leucocidin), can cause necrotising CAP, which is associated with high mortality rates (56–75%) [7-11].

Ceftaroline, the active metabolite of the prodrug ceftaroline fosamil, is a broad-spectrum cephalosporin with bactericidal in vitro activity against common Gram-positive organisms, including methicillin-susceptible *S. aureus* (MSSA), MRSA and non-extended-spectrum β-lactamase-producing Enterobacteriaceae [12,13]. Ceftaroline fosamil (administered intravenously [IV]) is approved

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in Europe for the treatment of moderate-to-severe CAP and complicated skin and soft-tissue infections in adults and children aged > 2 months; it is approved for similar indications in the United States [12,13]. Approval of ceftaroline fosamil for the treatment of CAP was based on the phase 3 FOCUS 1 and FOCUS 2 trials (NCT00621504 and NCT00509106) [14,15]. In these double-blind, randomised trials conducted in hospitalised patients with Pneumonia Outcomes Research Team (PORT) risk class III–IV CAP, ceftaroline fosamil 600 mg every 12 h (q12h) demonstrated non-inferiority to ceftriaxone 1 g q24h, in terms of clinical cure rates at the test-of-cure (TOC) visit [14-16]. Furthermore, in a phase 3 non-inferiority with nested superiority trial (NCT01371838), ceftaroline fosamil was shown to be superior to ceftriaxone 2 g q24h [17]. As ceftriaxone is inactive against MRSA, the above trials excluded patients with confirmed or suspected MRSA infections [14,15,17].

The current review aimed to examine the prevalence of MSSA and MRSA in CAP, investigate the synergism between *S. aureus* and influenza infections, review CAP treatment guidelines, and critically appraise in vitro, clinical and real-world data for ceftaroline fosamil in *S. aureus* CAP.

2. Prevalence of *Staphylococcus aureus* in community-acquired pneumonia

Community-acquired pneumonia has an annual incidence of 1.54–1.7 per 1000 general adult population and an estimated mortality rate (CAP/severe CAP [PORT class IV–V]) of 5.2–10.6% and 8.2–31.1%, respectively [3,18]. The epidemiology of *S. aureus* CAP is unclear, complicating empiric selection of antibiotic therapy [4]. In up to 36% of severe CAP cases, no causative organism is identified, which suggests that the prevalence of *S. aureus* is underestimated [19,20]. To determine the microbiological aetiologies of CAP, the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases evaluated epidemiological data from several studies [7]. The prevalence of *S. aureus* CAP was 0–1% in the outpatient setting, < 4% in patients admitted to hospital, < 19% in patients admitted to the intensive care unit (ICU), and 7–29% in elderly hospitalised patients [7]. MRSA often presents with rapidly progressive, severe respiratory disease; 75.0% of patients have multilobar radiographic shadowing and 76.5% are admitted to the ICU [7,21]. Overall, reported mortality rates associated with *S. aureus* CAP vary from 20–75% [9,21-25].

The PORT risk classification (I–V) and the Pneumonia Severity Index score are clinical prognostic tools used to classify patients with CAP based on their percentage risk of death within 30 days [18,26]. Mortality ranges from 0.1–2.8% for class I–III patients and 8.2–31.1% for class IV–V patients; all-class mortality is 5.2–10.6% [18]. In a Centers for Disease Control and Prevention population-based surveillance study of adults with CAP requiring hospitalisation, 65% (n = 1475) were stratified to PORT risk class I–III and 35% (n = 784) to class IV–V. *Staphylococcus aureus* was identified in 1.0% of patients in PORT risk class I–III and 3.0% of patients in class IV–V [27].

A prospective observational study conducted in Spain (n = 3523 adult patients with CAP; n = 1463 with known aetiology) reported that MSSA/MRSA were each responsible for 1% of cases, with the majority of *S. aureus* cases being PORT risk class IV (40.0%) [28]. The MSSA and MRSA mortality rates increased with PORT risk class; IV: 20.0% and V: 50.0% (identical values for MSSA and MRSA) [28]. For comparison, the mortality rate for patients infected with *Streptococcus pneumoniae* (n = 132) PORT risk class V was 23% [28].

In a multicentre, prospective cohort surveillance substudy of the Centers for Disease Control and Prevention Etiology of Pneumonia in the Community (EPIC) study, of 2259 hospitalised adult patients with CAP, 1.6% (n = 37) had *S. aureus* CAP, including 0.7% (n = 15) with MRSA and 1.0% (n = 22) with MSSA [4]. Despite the prevalence of MRSA CAP being 0.7%, 29.8% of patients received vancomycin or linezolid within 3 days of hospital admission [4]. In critically ill patients with CAP, empiric anti-MRSA therapy is an important consideration prior to diagnostic confirmation of the causative pathogen, as failure to cover for MRSA is associated with poor clinical outcomes [4]. *Staphylococcus aureus* CAP was associated with worse severity relative to other CAP types; 73.3% (n = 11) of patients with MRSA CAP and 50.0% (n = 11) of patients with MSSA CAP, respectively, were categorised to PORT risk class of IV or V, compared with 45.2% (n = 52) of patients with pneumococcal CAP and 34.3% (n = 762) of patients with all non-*S. aureus* CAP [4].

The aforementioned studies evaluated patients with culture-positive and culture-negative pneumonia. In a retrospective cohort study of 4543 patients with culture-positive pneumonia admitted into 59 American acute care hospitals between 2002–2003, 48.9% (n = 2221) had CAP [29]. Among these patients, the prevalence of MSSA, MRSA and all *S. aureus* was 17.2%, 8.9% and 25.5%, respectively, suggesting a higher prevalence of *S. aureus* in patients with CAP where a causative agent can be identified [29].

These prevalence data highlight the need for greater understanding of *S. aureus* CAP epidemiology, and the degree to which *S. aureus* is associated with severe disease versus other common CAP pathogens.

3. Interplay between *Staphylococcus aureus* and influenza

Patients infected with influenza A virus can develop secondary or concurrent *S. aureus* pneumonia [23,24,30-32]. This potential interaction between the two infections was highlighted in a 2.5-year surveillance study, in which *S. aureus* CAP cases occurred sporadically throughout the year, with two peaks of increased activity coinciding with seasonal influenza peaks (Fig. 1) [4]. The pathogenesis of influenza-associated *S. aureus* pneumonia is distinct from typical CAP: it is characterised as fulminant, with short intervals between onset of illness and diagnosis (< 7 days), rapid progression to severe disease (< 24 h) and where fatal, death occurs rapidly [33].

A synergistic relationship exists between *S. aureus* and influenza, whereby influenza A virus can induce an increase in *S. aureus*-specific adhesions throughout the respiratory tract and increase the number of *S. aureus*-specific proteases, which can enhance influenza virus replication [34-36]. Moreover, strains of influenza A virus can modulate the type 1 interferon response, decreasing the production of interleukin-1β and IL-23 (modulating levels of IL-10, IL-17, IL-22 and IL-27), leading to diminished alveolar macrophage and neutrophil phagocytosis of *S. aureus*, reduced production of antimicrobial peptides and, ultimately, increased host susceptibility to a secondary bacterial superinfection [37-43].

Epidemiological reports show that 20.0–83.7% of the overall population carry *S. aureus* in nasal passages, which is a risk factor for secondary *S. aureus* pneumonia in those with influenza A virus [44-47]. Colonising commensal bacteria establish mature biofilms on nasal tissue, encasing cells in a polymer-based matrix, enabling *S. aureus* to resist immune defences and decrease susceptibility to antimicrobial therapy [48-52]. In a study evaluating the transition of *S. aureus* from asymptomatic nasal colonisation to pneumonia, mice were intranasally inoculated with *S. aureus* only (control) or *S. aureus* and subsequently influenza A virus [50]. In co-infected mice, *S. aureus* dispersed from the biofilm state and developed secondary pneumonia, with high bacterial burdens recovered from lung tissue and overt signs of morbidity compared with the control group, highlighting the propensity of *S. aureus* to transform from commensal to pathogen in the presence of influenza A virus infection [50].

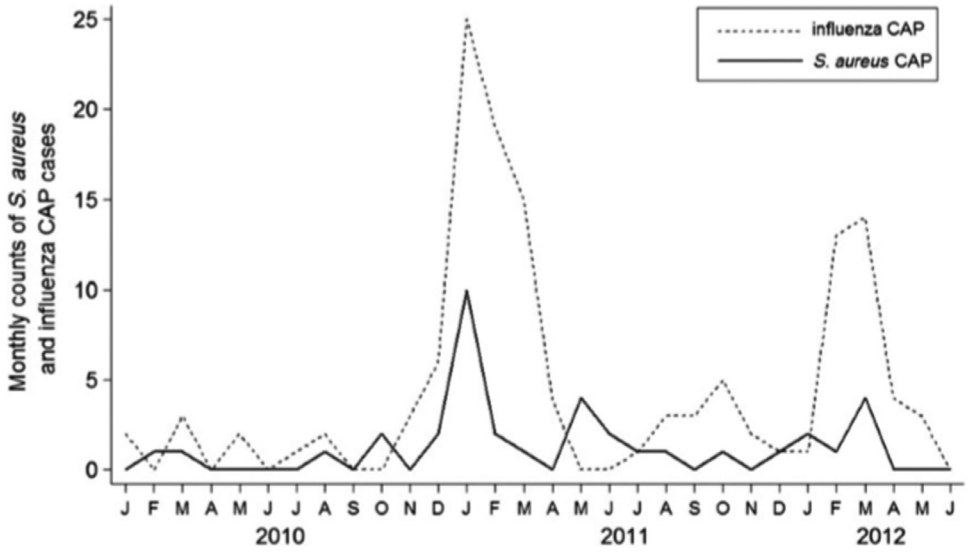

Fig. 1. Association of *Staphylococcus aureus* and influenza [4].
Image shows the counts of *S. aureus* and influenza community-acquired pneumonia (CAP) hospitalisations by month.
Single letters represent months of the year.

The association of *S. aureus* with influenza has also been seen in previous influenza pandemics. During the 1968–1969 influenza pandemic caused by influenza A virus subtype H3N2, among 108 patients with bacterial CAP presenting at the Grady Memorial Hospital (United States), *S. aureus* was the sole aetiological pathogen in 19.4% (n = 21). In the preceding non-pandemic year at the same institution, among 167 patients with CAP, *S. aureus* was the sole pathogen in 6% (n = 10) [32,53]. The median age of the 21 patients with *S. aureus* CAP was 43 years, which was 10 years younger than the overall cohort and 22 years younger than patients with *S. aureus* CAP admitted during 1967–1968 [32]. Only 43% of patients with *S. aureus* CAP presenting in 1968–1969 had co-morbidities versus 100% in 1967–1968, suggesting that influenza-associated *S. aureus* CAP often affects younger patients without co-morbidities [32].

During the United States 2003–2004 influenza season (predominated by influenza A virus subtype H3N2), one investigation reported 6010 cases of laboratory-confirmed influenza in adult patients, 97 (1.6%) of whom had secondary bacterial infections [53]. Almost half (n = 47; 48%) required mechanical ventilation and 17 (18%) died [53]. The most frequently isolated pathogen was *S. aureus* (n = 31; 32.0%), with MRSA (n = 24; 77.4%) predominating [53].

The 2006–2007 influenza season was predominated by influenza A virus subtype H1N1 in the United States [31,54]. Between November 2006 and April 2007, 51 cases of *S. aureus* CAP were reported to the Centers for Disease Control and Prevention from 19 states; 44 were identified by a positive culture result, four were identified by immunohistochemistry at autopsy, and three were identified by both [31]. The median age of patients was 16 years, and 56% had no underlying co-morbidities [31]. Of the culture-positive patients (n = 37 MRSA, n = 10 MSSA), 47% (n = 22) were diagnosed with a concurrent or antecedent viral infection, and of the 33 patients that were tested, 11 were positive for influenza [31]. Among the 47 patients for whom outcome information was available, a high mortality rate of 51% (n = 24) was observed; the median time from symptom onset to death was 4 days [31]. This case series highlights the need for vigilance during the influenza season for the development of *S. aureus* CAP in individuals without typical risk factors, based on the poor prognosis associated with influenza-associated *S. aureus* CAP [31,55].

4. Treatment guidelines for *Staphylococcus aureus* community-acquired pneumonia

The majority of patients with CAP are diagnosed based on clinical signs and symptoms, and are empirically treated with antibiotics; in approximately 35.5–58.0% of cases, an aetiological diagnosis is not possible [56-62]. Accordingly, empiric therapy needs to cover the most likely causative pathogens without providing excessively broad antimicrobial activity (to minimise the rise in antimicrobial resistance) and is typically guided by clinical presentation, consideration of risk factors, and knowledge of local epidemiology and antimicrobial susceptibility patterns [18,63,64]. A delay in the administration of appropriate empiric antibiotic therapy is associated with longer duration of hospitalisation, greater 30-day hospital readmission rates, increased healthcare costs, and increased mortality [65,66].

International treatment guidelines for moderate-to-severe CAP include European Respiratory Society/European Society for Clinical Microbiology and Infectious Diseases [7], British Thoracic Society [67], Infectious Diseases Society of America [68], and Chinese Thoracic Society/Chinese Medical Association [69]. With the exception of the latter, these guidelines are > 5 years old at the time of writing; updates are needed to reflect new evidence. The key points of each of the antimicrobial agents commonly used for the treatment of CAP are detailed in Table 1. Currently, all major guidelines recommend empirically starting a respiratory fluoroquinolone (such as levofloxacin or moxifloxacin) or a β-lactam (such as amoxicillin, ampicillin, amoxicillin-clavulanate, ampicillin-sulbactam, cefotaxime or ceftriaxone) plus a macrolide (azithromycin or clarithromycin) [7,67-69]. For patients with severe CAP requiring admission to the ICU, in the absence of risk factors for *Pseudomonas aeruginosa*, some guidelines recommend a β-lactam plus either a macrolide or a respiratory fluoroquinolone [7,68]. The aforementioned empiric therapy does not provide adequate coverage against MRSA CAP [70-78]. Where MRSA is suspected, regimens are typically supplemented with an anti-MRSA antibiotic – usually linezolid or vancomycin [68]. Empiric antibiotic therapy choices for CAP may need to change in the future, due to the increasing prevalence of MRSA CAP [79]. On confirmation of *S. aureus* as the aetiological pathogen, recommended antibiotics for MSSA CAP include

Table 1
Antimicrobial agents commonly used for the treatment of moderate-to-severe community-acquired pneumonia.

Antimicrobial	Class	Route of administration	PK	CAP indication	Special efficacy considerations	Special safety considerations
Amoxicillin/ clavulanic acid [128,129]	β-lactam	IV or oral	• Amoxicillin and clavulanic acid are well absorbed after oral dosing. The absolute bioavailability of oral amoxicillin and clavulanic acid is ~70% • Plasma protein binding: clavulanic acid ~25%; amoxicillin ~18% • Plasma elimination half-life: ~1 h • ~60–70% of amoxicillin and ~40–65% of clavulanic acid are excreted unchanged in urine • Clearance decreases proportionately with decreasing renal function. The reduction in drug clearance is more pronounced for amoxicillin than for clavulanic acid, as a greater proportion of amoxicillin is excreted via the renal route	Moderate-to-severe CAP caused by: • *S. pneumoniae*; MSSA; *H. influenzae; M. catarrhalis*	• Amoxicillin/clavulanic acid is not suitable for use when there is a high risk that the presumptive pathogens have reduced susceptibility or resistance to β-lactam agents that are not mediated by β-lactamases susceptible to inhibition by clavulanic acid • Prolonged use may occasionally result in overgrowth of non-susceptible organisms	**Contraindications** • Hypersensitivity to any penicillin • History of severe hypersensitivity to any other type of β-lactam agent • History of jaundice and/or hepatic impairment due to amoxicillin/clavulanic acid **Warnings and precautions** • Convulsions may occur in patients with impaired renal function or receiving high doses • Amoxicillin/clavulanic acid should be avoided if infectious mononucleosis is suspected • Concomitant use of allopurinol during treatment with amoxicillin can increase the likelihood of allergic skin reactions • The occurrence at the treatment initiation of a feverish generalised erythema associated with pustula may be a symptom of acute generalised exanthemous pustulosis • Amoxicillin/clavulanic acid should be used with caution in patients with evidence of hepatic impairment • Prolongation of prothrombin time has been rarely reported in patients receiving amoxicillin/clavulanic acid • In patients with renal impairment, the dose should be adjusted according to the degree of impairment • In patients with reduced urine output, crystalluria has very rarely been observed, predominantly with parenteral therapy
Ceftriaxone [130,131]	β-lactam	IV	• Plasma protein binding: ~85–95% • Plasma elimination half-life: ~8 h • 50–60% is excreted unchanged in the urine, primarily by glomerular filtration, while 40–50% is excreted unchanged in the bile • In patients with renal or hepatic dysfunction, the PK is only minimally altered • In older people aged > 75 y, the average elimination half-life is usually two to three times that of young adults	Moderate-to-severe CAP caused by: • *S. pneumoniae*; MSSA; *H. influenzae; H. parainfluenzae; K. pneumoniae; E. coli; Enterobacter aerogenes; Proteus mirabilis; Serratia marcescens*	• Ceftriaxone has a limited spectrum of antibacterial activity and may not be suitable for use as a single agent for the treatment of some types of infections unless the pathogen has already been confirmed • In polymicrobial infections, where suspected pathogens include organisms resistant to ceftriaxone, administration of an additional antibiotic should be considered	**Contraindications** • Hypersensitivity to ceftriaxone or to any other cephalosporin • History of severe hypersensitivity to any other type of β-lactam agent **Warnings and precautions** • Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form • Potential risk of haemolytic anaemia • Cases of pancreatitis, possibly of biliary obstruction aetiology, have been reported in patients treated with ceftriaxone • Cases of renal lithiasis have been reported, which are reversible upon discontinuation of ceftriaxone

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Table 1 (*continued*)

Antimicrobial	Class	Route of administration	PK	CAP indication	Special efficacy considerations	Special safety considerations
Ceftaroline fosamil [12,13]	β-lactam	IV	• Rapidly metabolised to active ceftaroline upon IV administration • Plasma protein binding: ~20% • Plasma elimination half-life: ~2.5 h • Ceftaroline is primarily eliminated by the kidneys; ~88% excreted in urine • Dosage adjustments are required in patients with CrCl ≤ 50 mL/min • PK of ceftaroline were similar between healthy elderly subjects (≥ 65 y), and healthy young adult subjects (18–45 y)	Moderate-to-severe CAP caused by: • *S. pneumoniae*; MSSA; *E. coli; H. influenzae; H. parainfluenza; K. pneumoniae*	• There is no experience with ceftaroline fosamil in the treatment of CAP in the following patient groups: the immunocompromised, patients with severe sepsis/septic shock, severe underlying lung disease, those with PORT risk class V, and/or CAP requiring ventilation at presentation, CAP due to MRSA or patients requiring intensive care	**Contraindications** • Hypersensitivity to the cephalosporin class of antibiotics • Immediate and severe hypersensitivity to any other type of β-lactam **Warnings and precautions** • Serious and occasionally fatal hypersensitivity reactions are possible • Non-susceptible organisms: superinfections may occur during or following treatment • Patients with pre-existing seizure disorder: seizures have occurred in toxicology studies at 7–25 times human ceftaroline C_{max} levels. As clinical study experience with ceftaroline fosamil in patients with pre-existing seizure disorders is very limited, it should be used with caution in this patient population • Potential risk of haemolytic anaemia: in clinical studies there was no evidence of haemolysis in patients who developed a positive direct antiglobulin test on treatment. However, the possibility that haemolytic anaemia may occur in association with cephalosporins, including ceftaroline fosamil treatment, cannot be ruled out. Patients experiencing anaemia during or after treatment should be investigated for this possibility
Moxifloxacin [132,133]	Fluoroquinolone	IV or oral	• Well absorbed after oral dosing. The absolute bioavailability of oral moxifloxacin is ~90% • Plasma protein binding: 30–50% • Plasma elimination half-life: 12 ± 1.3 h • Approximately ~45% excreted as unchanged drug (~20% in urine and ~25% in faeces) • No significant differences in PK between young and elderly subjects • PK not significantly altered in patients with any degree of renal impairment	Moderate-to-severe CAP caused by: • *S. pneumoniae*; MSSA; *H. influenzae; K. pneumoniae; Mycoplasma pneumoniae; M. catarrhalis; Chlamydophila pneumoniae*	• Moxifloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of CAP • MRSA is very likely to possess co-resistance to fluoroquinolones, including moxifloxacin	**Contraindications** • Hypersensitivity to moxifloxacin or other quinolones **Warnings and precautions** • Risk of tendinitis and tendon rupture is increased. Discontinue immediately if the patient experiences pain, swelling, inflammation or rupture of a tendon • Moxifloxacin has been associated with an increased risk of peripheral neuropathy. Avoid in patients who have previously experienced peripheral neuropathy • Prolongation of the QT interval and isolated cases of torsade de pointes have been reported. Avoid use in patients with known prolongation, proarrhythmic conditions such as clinically significant bradycardia or acute myocardial ischaemia, hypokalaemia, hypomagnesemia, and with drugs that prolong the QT interval

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Table 1 (*continued*)

Antimicrobial	Class	Route of administration	PK	CAP indication	Special efficacy considerations	Special safety considerations
						• Moxifloxacin has been associated with an increased risk of central nervous system reactions, including convulsions and increased intracranial pressure (including pseudotumor cerebri) and toxic psychosis • Moxifloxacin may exacerbate muscle weakness in patients with myasthenia gravis. Avoid in patients with known history of myasthenia gravis • Hypersensitivity and other serious reactions: serious and sometimes fatal reactions, including anaphylactic reactions, may occur after first or subsequent doses of moxifloxacin
Levofloxacin [134,135]	Fluoroquinolone	IV or oral	• Extensively absorbed after oral dosing. Maximum plasma concentrations are reached ~1–2 h after dosing and absolute bioavailability is ~99% • Plasma protein binding: ~24–38% • Plasma elimination half-life: 6–8 h • Excretion is primarily by the renal route (> 85 % of the administered dose) • No significant differences in PK between young and elderly subjects when differences in CrCl are taken into consideration • Clearance is substantially reduced, and plasma elimination half-life is substantially prolonged in adult patients with impaired renal function (CrCl < 50 mL/min)	Moderate-to-severe CAP caused by: • *S. pneumoniae*; MSSA; *H. influenzae; H. parainfluenzae; K. pneumoniae; M. catarrhalis; Chlamydophila pneumoniae; Legionella pneumophila; Mycoplasma pneumoniae*	• Levofloxacin should be used only when it is considered inappropriate to use antibacterial agents that are commonly recommended for the initial treatment of CAP (except severe cases) or when these have failed • MRSA is very likely to possess co-resistance to fluoroquinolones, including levofloxacin	**Contraindications** • Hypersensitivity to levofloxacin or other quinolones **Warnings and precautions** • Risk of tendinitis and tendon rupture is increased. Discontinue if pain or inflammation in a tendon occur • Anaphylactic reactions and allergic skin reactions, serious, occasionally fatal, may occur after first dose • Haematological (including agranulocytosis, thrombocytopenia), and renal toxicities may occur after multiple doses • Severe, and sometimes fatal, hepatoxicity has been reported. Discontinue immediately if signs and symptoms of hepatitis occur • Central nervous system effects, including convulsions, anxiety, confusion, depression, and insomnia may occur after the first dose. Use with caution in patients with known or suspected disorders that may predispose them to seizures or lower the seizure threshold • Peripheral neuropathy: discontinue if symptoms occur in order to prevent irreversibility • Prolongation of the QT interval and isolated cases of torsade de pointes have been reported. Avoid use in patients with known prolongation, those with hypokalaemia, and with other drugs that prolong the QT interval

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Table 1 (*continued*)

Antimicrobial	Class	Route of administration	PK	CAP indication	Special efficacy considerations	Special safety considerations
Linezolid [136,137]	Oxazolidinone	IV or oral	• Extensively absorbed after oral dosing. Maximum plasma concentrations are reached ~1–2 h after dosing and absolute bioavailability is ~100% • Plasma protein binding: 31% • Plasma elimination half-life: 5–7 h • Non-renal clearance accounts for ~65% of the total clearance of linezolid • PK not significantly altered in elderly patients ≥ 65 y or in patients with any degree of renal impairment	CAP caused by: • *S. pneumoniae* including cases with concurrent bacteraemia • Susceptible isolates of MRSA	• Linezolid is indicated in adults for the treatment of CAP when known or suspected to be caused by susceptible Gram-positive bacteria. Linezolid is not active against infections caused by Gram-negative pathogens. Specific therapy against Gram-negative organisms must be concomitantly initiated if a Gram-negative pathogen is documented or suspected	**Contraindications** • Linezolid should not be used in patients taking any medicinal product that inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid) or within 2 weeks of taking any such medicinal product • Contraindicated for use in patients who have known hypersensitivity to linezolid or any of the other product components. **Warnings and precautions** • Myelosuppression: monitor complete blood counts weekly • Peripheral and optic neuropathy • Serotonin syndrome: patients taking serotonergic antidepressants should receive linezolid only if no other therapies are available • A mortality imbalance was seen in an investigational study in linezolid treated patients with catheter-related bloodstream infections • Potential interactions producing elevation of blood pressure: monitor blood pressure • Post-marketing cases of symptomatic hypoglycaemia have been reported in patients with diabetes mellitus receiving insulin or oral hypoglycaemic agent
Vancomycin [138,139]	Glycopeptide	IV	• Plasma protein binding: 30–55% • Plasma elimination half-life: 4–6 h • In the first 24 h after IV administration, ~75–80% of an administered dose of vancomycin is excreted in urine by glomerular filtration • Total body and renal clearance of vancomycin may be reduced in the elderly • Renal impairment slows excretion of vancomycin	CAP caused by: • *S. pneumoniae* including cases with concurrent bacteraemia • Susceptible isolates of MRSA • MSSA in patients allergic to penicillin, or those patients who cannot receive or who have failed to respond to other drugs	• Vancomycin has a spectrum of antibacterial activity limited to Gram-positive organisms	**Contraindications** • Hypersensitivity to vancomycin **Warnings and precautions** • Nephrotoxicity: systemic vancomycin exposure may result in acute kidney injury, including acute renal failure, mainly due to interstitial nephritis or less commonly acute tubular necrosis. Monitor serum vancomycin concentrations and renal function • Ototoxicity has occurred in patients receiving vancomycin. Monitor for signs and symptoms of ototoxicity during therapy • Neutropenia: periodically monitor leukocyte count. • Development of drug-resistant bacteria: prescribing vancomycin in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria

IV, intravenous; CAP, community-acquired pneumonia; *S. pneumoniae, Streptococcus pneumoniae*; MSSA, methicillin-susceptible *Staphylococcus aureus; H. influenzae, Haemophilus influenzae; H. parainfluenzae, Haemophilus parainfluenzae; E. coli, Escherichia coli*; PK, pharmacokinetic; PORT, Pneumonia Outcomes Research Team; MRSA, methicillin-resistant *Staphylococcus aureus; K. pneumoniae, Klebsiella pneumoniae; M. catarrhalis, Moraxella catarrhalis*

anti-staphylococcal penicillins (such as oxacillin and flucloxacillin), with vancomycin and linezolid suggested for MRSA CAP [67-69].

Although vancomycin is the standard of care for MRSA CAP, several studies have reported suboptimal treatment results, with treatment failure attributed to sub-therapeutic penetration into lung parenchyma, as determined from concentrations in epithelial lining fluid (ELF) relative to plasma [80-83]. Moreover, vancomycin is associated with nephrotoxicity at higher concentrations and does not inhibit production of bacterial toxins, such as Panton–Valentine leucocidin [84-87].

Head-to-head data evaluating the clinical effectiveness of vancomycin and linezolid for the treatment of MRSA CAP are lacking, as no comparative trials in the CAP population have been carried out to date. Animal and human pharmacokinetic (PK) data suggest that linezolid has advantages over vancomycin for treating MRSA pneumonia, due to higher ELF penetration and inhibition of bacterial toxin production [88-91]. In a phase 4 trial, hospitalised patients (n = 1184) with MRSA hospital-acquired pneumonia or healthcare-associated pneumonia were randomised to receive linezolid (600 mg q12h) or vancomycin (15 mg/kg q12h) for 7–14 days [92]. Clinical cure rates in the per-protocol population at the end of study were significantly higher ($P = 0.042$) for linezolid (57.6%) than for vancomycin (46.6%), despite all-cause 60-day mortality in the intention-to-treat population being similar (linezolid 15.7%, vancomycin 17.0%) [92]. A meta-analysis of randomised controlled trials comparing vancomycin or teicoplanin with linezolid for the treatment of hospital-acquired pneumonia demonstrated no significant difference in clinical cure or all-cause mortality. Linezolid was associated with a greater risk of gastrointestinal events, whereas renal dysfunction and rash were more common with vancomycin [93]. The relevance of these comparative clinical data for the treatment of CAP is unknown.

In the clinical setting, β-lactams represent the empiric treatment of choice for CAP; however, available susceptibility data indicate that these agents do not adequately cover *S. aureus*, thus highlighting the need for alternative treatment options.

5. Ceftaroline fosamil for *Staphylococcus aureus* community-acquired pneumonia

5.1. Ceftaroline fosamil

Similar to other β-lactam antibiotics, ceftaroline exerts its bactericidal effect by binding to penicillin-binding proteins (PBPs), resulting in impaired bacterial cell wall synthesis, cell lysis and death [13,94,95]. The key determinant rendering MRSA resistant to most β-lactam antibiotics is PBP2a (encoded by the *mecA* gene), which has low affinity for this antibiotic class [96,97]. Unlike other β-lactam antibiotics (with the exception of ceftobiprole), ceftaroline has high binding affinity for PBP2a, as demonstrated by in vitro minimum inhibitory concentrations (MIC) required to inhibit 50% (MIC_{50}) and 90% (MIC_{90}) of *S. aureus* isolates. Against MSSA isolates, ceftaroline has an $MIC_{50/90}$ of 0.25 g/L; against MRSA, ceftaroline has an MIC_{50} of 0.5 g/L and an MIC_{90} of 1–2 g/L [94,98-100]. Consequently, ceftaroline fosamil may be effective against both MSSA and MRSA CAP [94,101].

5.2. Assessing Worldwide Antimicrobial Resistance and Evaluating surveillance data

In vitro activities of ceftaroline and ceftriaxone were compared against clinical isolates of *S. aureus* (n = 18 078) collected from 37 countries during 2014–2015 as part of the Assessing Worldwide Antimicrobial Resistance and Evaluation (AWARE) programme [99]. Ceftaroline was ≥ 16-fold more potent than ceftriaxone against MSSA (MIC_{90} 0.25 mg/L vs. 4 mg/L), and ≥ 32-fold more potent than ceftriaxone against MRSA (MIC_{90} 1 mg/L vs. > 32 mg/L) (Table 2). At the European Committee on Antimicrobial Susceptibility Testing (EUCAST) MIC susceptibility breakpoint (≤ 1 mg/L) for ceftaroline, 100.0% of MSSA and 90.2% of MRSA isolates were inhibited by ceftaroline [99]. Similarly, in vitro activities of ceftriaxone and ceftaroline were compared against clinical isolates (n = 13 005) collected from 39 countries (Asia-Pacific, Europe, Latin America and Africa-Middle East) during 2012–2014 [98]. Compared with ceftriaxone, ceftaroline was > 16-fold more potent against MSSA (MIC_{90} 0.25 mg/L vs. 4 mg/L) and ≥ 16-fold more potent against MRSA (MIC_{90} 2 mg/L vs. > 32 mg/L) [98].

5.3. Pharmacokinetics and pharmacodynamics

The prodrug ceftaroline fosamil is rapidly dephosphorylated into active ceftaroline following IV administration [13,102]. Ceftaroline has a linear pharmacokinetics (PK) profile with maximum plasma concentration (C_{max}) and area under the concentration–time (AUC) curve increases occurring approximately in proportion to dose increases within the range of 50–1000 mg [13]. Following a single 600 mg IV dose of radiolabelled ceftaroline fosamil, the median steady-state volume of distribution of ceftaroline in healthy adult males was found to be 20.3 L [13]. Plasma protein binding of ceftaroline is approximately 20%, and terminal elimination half-life approximately 2.5 hours; the primary elimination route for ceftaroline is renal excretion, with a small proportion converted to the inactive metabolite ceftaroline-M1 [13].

Pharmacokinetic/pharmacodynamic (PK/PD) targets for ceftaroline have been derived from a range of in vitro and in vivo studies [103-105]. Mean % $fT_{>MIC}$ values from these studies for *S. aureus* were 27% for stasis, 31% for 1-log_{10} reduction, and 35% for 2-log_{10} reduction [106]. Using the above targets, a population PK analysis including subject PK data from 17 clinical studies evaluated the impact of various factors on ceftaroline exposures; ethnicity was not found to be a significant covariate when corrected for body weight, suggesting comparable ceftaroline exposures in Asian and Western populations [107]. Based on this model, for 5000 simulated Asian patients with CAP receiving ceftaroline fosamil 600 mg q12h, probability of target attainment was > 98% for the above *S. aureus* PK/PD targets at ceftaroline MICs ≤ 2 mg/L [107].

A further population PK model for ceftaroline and ceftaroline fosamil developed using PK data from 21 clinical studies was used to simulate exposures and probability of target attainment in 5000 patients with complicated skin and soft-tissue infection receiving ceftaroline fosamil 600 mg q12h or 600 mg q8h [106]. Using the above PK/PD targets, high probability of target attainments (> 90%) were predicted for both ceftaroline fosamil dosage regimens against *S. aureus* isolates with ceftaroline MICs ≤ 2 mg/L [106,108].

In a neutropenic murine lung model, the pharmacokinetics of a human-simulated ceftaroline fosamil regimen of 600 mg q12h were evaluated in serum and ELF against 17 *S. aureus* isolates (two MSSA, 15 MRSA) with ceftaroline MICs of 0.5–4 mg/L [109]. Overall, 41.0% $fT_{>MIC}$ was required to produce a 1-log_{10} kill, and 16.0% $fT_{>MIC}$ was required for stasis [109]. The $fT_{>MIC}$ of 41.0% required to produce a 1-log_{10} kill in the above model was greater than that observed in a previous study that evaluated human-simulated exposures of ceftaroline fosamil 600 mg q12h in serum against 26 *S. aureus* isolates (four MSSA, 22 MRSA; ceftaroline MICs: 0.125–4 mg/L) in neutropenic and immunocompetent mouse thigh infection models [110]. In this study, a mean $fT_{>MIC}$ of 19.3% resulted in a 1-log_{10} reduction in bacterial density [110].

Table 2
Overview from key studies of in vitro activity and clinical response rates of ceftaroline fosamil and ceftriaxone against *Staphylococcus aureus* in community-acquired pneumonia [14,15,17,99].

		Ceftaroline fosamil	Ceftriaxone
In vitro studies	MIC_{90} values against 7498 MSSA isolates and 10 580 MRSA isolates		
	AWARE programme	MSSA: MIC_{90} 0.25 mg/L	MSSA: MIC_{90} 4 mg/L
		MRSA: MIC_{90} 1 mg/L	MRSA: MIC_{90} 32 mg/L
Clinical studies	Clinical response rates at TOC against *S. aureus* in the ME population		
	FOCUS 1, n/N (%)	8 of 10 (80.0)	7 of 12 (58.3)
	FOCUS 2, n/N (%)	10 of 15 (66.7)	8 of 15 (53.3)
	ASIA CAP, n/N (%)	4 of 4 (100.0)	2 of 4 (50.0)
	Pooled, n/N (%)	22 of 29 (75.9)	17 of 31 (54.8)

S. aureus, *Staphylococcus aureus*; ME, microbiologically evaluable; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-sensitive *S. aureus*; AWARE, Assessing Worldwide Antimicrobial Resistance and Evaluation; TOC, test-of-cure

5.4. Pharmacokinetics in special patient populations

There is a paucity of ceftaroline PK data for special patient populations specific to CAP; however, various PK analyses were undertaken for several subpopulations in the COVERS trial (NCT01499277), which evaluated ceftaroline fosamil 600 mg q8h in patients with complicated skin and soft-tissue infections [111]. For 366 patients with evaluable PK data, ceftaroline exposures – including maximum plasma concentration at steady state ($C_{max,ss}$) and area under the plasma concentration–time curve for 0–8 h at steady state ($AUC_{0-8,ss}$) – were summarised by the following subgroups indicative of baseline disease severity: fever ($\leq$ 38°C or $>$ 38°C), white blood cell count ($\leq$ 12 000/mm^3 or $>$ 12 000/mm^3), C-reactive protein ($\leq$ 50 mg/L, $>$ 50 to $\leq$ 150 mg/L or $>$ 150 mg/L), and absence or presence of systemic inflammatory response syndrome or bacteraemia [112,113]. The $AUC_{0-8,ss}$ and $C_{max,ss}$ values overlapped in patients within the respective subgroups, indicating that these parameters had minimal impact on ceftaroline exposures [112,113].

Ceftaroline exposures were also explored in simulations of patients with augmented renal clearance and body mass index (BMI) categories: normal to overweight 18.5–29.9 kg/m^2; obese class I 30–34.9 kg/m^2; obese class II 35–39.9 kg/m^2; and obese class III $\geq$ 40 kg/m^2. These analyses indicated that augmented renal clearance and obesity have minimal impact on ceftaroline exposures [113].

5.5. Penetration of ceftaroline fosamil into the epithelial lining fluid

Pulmonary ELF and alveolar macrophages are important infection sites for common extracellular and intracellular respiratory pathogens, respectively; the extent of penetration of antimicrobials at these sites potentially correlates with clinical efficacy [114,115]. Thus, an understanding of ceftaroline concentrations in the ELF may be relevant for defining appropriate antimicrobial therapy and dosing regimens.

In a phase 1 study, 53 healthy subjects were randomised to receive ceftaroline fosamil 600 mg, either q12h or q8h for 3 days, followed by a single dose on day 4 [116]. The penetration of free ceftaroline into ELF, relative to total plasma concentrations, was 22.5% (600 mg q12h) and 23.6% (600 mg q8h), which is comparable with other β-lactams [116–119]. Using plasma and ELF exposure data, simulations evaluated achievement of $fT_{>MIC}$ targets of 42.0% for plasma and 17.0% for ELF [116]. For ceftaroline 600 mg q12h, 98.1% of simulated patients achieved a 42.0% $fT>$ 1 mg/L in plasma, and 81.7% achieved a 17.0% $fT>$ 1 mg/L in ELF [116]. For ceftaroline fosamil 600 mg q8h, 100% and 94.7% of simulated patients achieved the respective plasma and ELF targets [116]. At an MIC of 2 mg/L, 69.0% and 26.8% of simulated patients receiving ceftaroline fosamil 600 mg q12h achieved the respective plasma and ELF targets; for 600 mg q8h, 97.9% of simulated patients achieved the plasma target and 58.5% achieved the ELF target [116]. These data suggest that ceftaroline fosamil 600 mg q12h should be effective for treating *S. aureus* pneumonia with a ceftaroline MIC of $\leq$ 1 mg/L [116].

5.6. Ceftaroline fosamil in clinical trials

FOCUS 1 and FOCUS 2, the pivotal phase 3 studies of ceftaroline fosamil in adult patients with radiologically confirmed moderate-to-severe CAP (PORT risk class III or IV), compared ceftaroline fosamil 600 mg q12h with ceftriaxone 1 g/day (patients in FOCUS 1 received adjunctive empiric macrolide therapy on day 1 for atypical pathogen coverage) [14,15]. A subsequent phase 3 non-inferiority with nested superiority trial in Asian patients with CAP used a similar design to FOCUS 1 and FOCUS 2, but with ceftriaxone 2 g/day as a comparator [17]. Patients with confirmed MRSA or risk factors for MRSA were excluded from these trials, owing to the inactivity of ceftriaxone against MRSA [14,15,17].

In the individual FOCUS 1 and FOCUS 2 trials, ceftaroline fosamil was well tolerated and demonstrated non-inferiority to ceftriaxone in the co-primary modified intent-to-treat efficacy and clinically evaluable populations for the primary endpoint of clinical cure at the TOC visit (8–15 days after the last dose of study treatment) [14,15]. Macrolide therapy for atypical pathogen in FOCUS 1 did not significantly affect clinical outcomes [14,16]. In the integrated analysis of FOCUS 1 and FOCUS 2, clinical cure rates for patients with MSSA CAP at the TOC visit in the microbiological modified intent-to-treat efficacy population were 72% (18 of 25) with ceftaroline fosamil, compared with 60% (18 of 30) for ceftriaxone [16]. The integrated analysis of FOCUS 1 and FOCUS 2 provided a safety data set of 1228 patients, with ceftaroline fosamil demonstrating a favourable safety and tolerability profile, as expected for a cephalosporin, with similar rates of adverse events (AEs) for ceftaroline fosamil (47.0%) and ceftriaxone (45.7%) [16]. The most frequently reported AEs were diarrhoea (4.2%), headache (3.4%) and insomnia (2.3%) for patients treated with ceftaroline fosamil; and diarrhoea (2.6%), hypertension (2.6%) and hypokalaemia (2.4%) for patients treated with ceftriaxone [16]. The incidence of serious AEs was 11.3% for ceftaroline fosamil and 11.7% for ceftriaxone, with comparable rates of serious hepatobiliary (0.33% for ceftaroline fosamil vs. 0.81% for ceftriaxone), renal (0.33% for both groups), or haematological (0.33% vs. 0.0%) events [16].

In addition to clinical response assessments at the TOC visit, US Food and Drug Administration guidelines for the design of non-inferiority CAP trials recommend evaluation of clinical response 72–96 h after initiating therapy [120]. Thus, a retrospective post hoc analysis of day 4 response rates was carried out in 309 patients with microbiologically confirmed moderate-to-severe CAP enrolled in the FOCUS trials [120]. Day 4 clinical response rates in patients with MSSA were 58.3% (14 of 24) for ceftaroline fosamil and 54.8% (17 of 31) for ceftriaxone (exploratory MITT population),

providing further evidence of the viability of ceftaroline fosamil for the treatment of MSSA CAP [120].

The FOCUS 1 and FOCUS 2 trials included patients predominately from Europe and North America. Consequently, a further double-blind, phase 3, non-inferiority with nested superiority trial in adult Asian patients with moderate-to-severe CAP (PORT risk class III or IV) was undertaken [17]. Patients were randomised (1:1) to receive ceftaroline fosamil (600 mg q12h) or ceftriaxone (2 g q24h) for 5–7 days [17]. At the TOC visit (8–15 days after the last dose of study treatment), the difference in clinical cure rates for ceftaroline fosamil versus ceftriaxone met pre-defined superiority criteria in the clinically evaluable population [17]. Clinical cure rates for patients with MSSA CAP in the microbiologically evaluable population were 100% (4 of 4) with ceftaroline fosamil versus 50% (2 of 4) with ceftriaxone [17].

The similar designs of the FOCUS 1, FOCUS 2, and Asian CAP trials, together with a distinct lack of heterogeneity, enabled pooling of the microbiological data from all three randomised trials. In patients with MSSA CAP, results of the pooled analysis favoured ceftaroline fosamil over ceftriaxone, with clinical response rates at the TOC visit (microbiologically evaluable population) of 75.9% (22 of 29) versus 54.8% (17 of 31) (Table 2) [121].

5.7. Clinical Assessment Program and Teflaro Utilization Registry study

Clinical Assessment Program and Teflaro Utilization Registry (CAPTURE) is a multicentre, retrospective database study designed to collect information on patients receiving ceftaroline fosamil in the United States [122]. The generated data provide important insights into the real-world therapeutic effectiveness of ceftaroline fosamil for a number of indications, including CAP, and in patient populations (i.e. MRSA) that were excluded from phase 3 clinical trials [123].

Between August 2011 and February 2013, data collected for CAPTURE included 398 evaluable patients with CAP; 76% of these patients had co-morbidities including structural lung disease (41%), history of smoking (29%), prior pneumonia (25%), gastroesophageal reflux disease (23%), and congestive heart failure (20%) [122]. Pathogen identification was available in 40% of patients, with *S. aureus* accounting for 22% of all isolated pathogens (MSSA 16%, MRSA 6%) [122]. Clinical success rates with ceftaroline fosamil were 68% (58 of 85) in patients with culture-positive *S. aureus*, 66% (42 of 64) in patients with MRSA, and 74% (17 of 23) in patients with MSSA [122].

From the same cohort of 398 patients with CAP, 21 hospitalised patients with secondary *S. aureus* bacteraemia (SAB) were identified, 76% (n = 16) of whom had MRSA CAP [124]. Following a mean duration of 7 days of treatment with ceftaroline fosamil, the clinical success rate for SAB secondary to MRSA CAP was 63% (10 of 16), and 80% (4 of 5) for SAB secondary to MSSA CAP [124]. The overall success rate among patients with SAB due to CAP was 67% (14 of 21) [124]. These data support the use of ceftaroline fosamil as a potential treatment option for hospitalised patients with SAB secondary to CAP.

To examine the use of ceftaroline fosamil in patients with renal insufficiency (RI), a further analysis of CAPTURE data was undertaken comprising 344 patients with CAP treated between August 2012 and February 2014. Pathogens were successfully isolated from 114 patients: 46 had MRSA and 20 had MSSA [125]. Clinical success in patients with MRSA CAP occurred in 83% (25 of 30) of patients with normal renal function or mild RI (CrCl > 50 mL/min), 60% (two of five) of patients with moderate RI (CrCl 31–50 mL/min), and 100% of patients with severe RI (CrCl 15–30 mL/min [nine of nine]) and end-stage renal disease (ESRD; CrCl < 15 mL/min [two of two]). In patients with MSSA CAP, clinical success occurred in 100% (11 of 11) of patients with normal renal function or mild RI, 50% (two of four) of patients with moderate RI, 50% (one of two) of patients with severe RI, and 100% (three of three) of patients with ESRD [125]. Overall, clinical success was achieved in 83% (38 of 46) and 85% (17 of 20) of patients with MRSA and MSSA CAP, respectively [125]. No patients with moderate or severe RI or ESRD discontinued ceftaroline fosamil due to an AE [125]. These results indicate that ceftaroline fosamil is an effective treatment option for *S. aureus* CAP in patients with impaired renal function.

The above CAPTURE analysis also evaluated the efficacy of ceftaroline fosamil in patients with CAP admitted to the ICU [125]. Although these results were not analysed by causative pathogen, the data are important as patients with MRSA CAP often present with severe respiratory disease requiring ICU admission [21]. Clinical success rates in ICU-treated patients with CAP were 82% (70 of 85), 67% (14 of 21), 73% (8 of 11) and 100% (four of four), for those with normal/mild RI, moderate RI, severe RI and ESRD, respectively [125]. This suggests that ceftaroline fosamil is an effective treatment option in patients with CAP admitted to the ICU.

In addition to the CAPTURE study, other investigators have reported observational and retrospective data pertaining to the use of ceftaroline fosamil in MRSA CAP. A retrospective study in a US hospital reviewing the use of ceftaroline fosamil in MRSA pneumonia comprised 25 patients with healthcare-associated pneumonia and six patients with CAP, and excluded those with < 7 days treatment duration [126]. Clinical success was achieved in 62% (19 of 31), treatment failure occurred in 19% (6 of 31), and 16% (5 of 31) had indeterminate clinical outcomes [126]. In seven patients (23%), ceftaroline fosamil was used as second-line treatment, with clinical success in five patients [126]. Although data for healthcare-associated pneumonia and CAP were not separately reported, these results corroborate the effectiveness of ceftaroline fosamil against MRSA pneumonia observed in the CAPTURE study. Taken together, these data from phase 3 trials and real-world studies suggest that ceftaroline fosamil is a viable alternative to current standard-of-care therapies for CAP caused by *S. aureus*, including both MRSA and MSSA.

5.8. Pharmacoeconomics

To assess the economic impact of adding ceftaroline fosamil to a US hospital formulary, a 3-year hospital budget impact model was constructed to evaluate patients hospitalised with CAP (PORT risk class III or IV) [127]. Patients were randomised to receive ceftaroline fosamil 600 mg q12h or ceftriaxone 1 g/day for 5–7 days, with assumed clinical cure rates based on the FOCUS 1 and 2 trials [127]. The estimated total cost for treating a patient with CAP with ceftaroline fosamil was $1102 lower ($18 925 vs. $20 027) than ceftriaxone (sensitivity analysis range: –$6 to –$2223) [127]. These data indicate that ceftaroline fosamil is a cost-effective treatment option when compared with a relevant antimicrobial standard-of-care therapy.

6. Conclusions

In CAP, the identity of aetiological pathogens is often unknown, with microbiological diagnosis available in a limited number of cases. This lack of diagnostic certainty complicates the epidemiological understanding of CAP and presents obstacles for optimal treatment. Although the available literature collectively suggests that the prevalence of *S. aureus* as a cause of CAP is relatively low, *S. aureus* CAP is associated with increased severity, morbidity and mortality, relative to other common forms of CAP. This increased severity is particularly notable for MRSA CAP, the frequency of which is increasing. For several decades, β-lactams have been the cornerstone of empiric CAP treatment. However, based on available

susceptibility data, the agents currently recommended for empiric therapy of moderate-to-severe CAP, including ceftriaxone, do not adequately cover *S. aureus*, particularly MRSA. Phase 3 clinical trials have shown ceftaroline fosamil to be a viable alternative to ceftriaxone for the treatment of moderate-to-severe *S. aureus* CAP, and available susceptibility data demonstrate broader coverage against *S. aureus*. Although ceftaroline fosamil has not been studied in prospective trials for the treatment of MRSA CAP (owing to the exclusion of such patients from pivotal trials), the evidence from in vitro and non-clinical studies and real-world data suggests that it is a potentially effective treatment option for MRSA CAP, as well as SAB secondary to CAP, while maintaining a safety and tolerability profile comparable with other antibiotics of the cephalosporin class.

Declarations

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Competing Interests

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Ethical Approval

Not required.

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