Review Article

New cephalosporins for the treatment of pneumonia in internal medicine wards

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Abstract: The burden of hospital admission for pneumonia in internal medicine wards may not be underestimated; otherwise, cases of pneumonia are a frequent indication for antimicrobial prescriptions. Community- and hospital-acquired pneumonia are characterized by high healthcare costs, morbidity and non-negligible rates of fatality. The overcoming prevalence of resistant gram-negative and positive bacteria (e.g., methicillin-resistant *Staphylococcus aureus*, penicillin and ceftriaxone-resistant *Streptococcus pneumoniae*, extended-spectrum β-lactamases and carbapenemases producing *Enterobacteriaceae*) has made the most of the first-line agents ineffective for treating lower respiratory tract infections. A broad-spectrum of activity, favourable pulmonary penetration, harmlessness and avoiding in some cases a combination therapy, characterise new cephalosporins such as ceftolozane/tazobactam, ceftobiprole, ceftazidime/avibactam and ceftaroline. We aimed to summarise the role and place in therapy of new cephalosporins in community- and hospital-acquired pneumonia within the setting of internal medicine wards. The "universal pneumonia antibiotic strategy" is no longer acceptable for treating lung infections. Antimicrobial therapy should be individualized considering local antimicrobial resistance and epidemiology, the stage of the illness and potential host factors predisposing to a high risk for specific pathogens.

Keywords: Cephalosporins; nosocomial pneumonia (NP); community-acquired pneumonia (CAP); methicillin-resistant *Staphylococcus aureus* (MRSA); influenza; multi-drug resistant bacteria

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Introduction

Pneumonia is one of the most common indications for the antibiotic prescription (19.2%), followed by skin and soft tissue infections (SSTIs; 9.0%) and intra-abdominal infections (IAIs; 7.0%) (1). Despite advances in clinical treatment and antibiotic therapy, pneumonia is still associated with high morbidity and mortality worldwide (2-4). The burden of hospital admissions for pneumonia is high (5-7): twenty-four to 75% of these patients are expected to be admitted in internal medicine wards (IMWs) (8-12). Community-acquired pneumonia (CAP) is associated with significant costs, high rate of hospitalization (3,4) and intensive care unit (ICU) admissions (2,5). Mortality rate is increased up to 40% by several factors, as older age or comorbidities (13). Nosocomial pneumonia (NP) accounts for approximately 25% of the total infections harbored in the ICU and such circumstances have an enormous effect on the length of hospital stay and hospital related cost, with a mortality of between 27% to 50% (14). The efficacy of the treatment is even more compromised in countries where antibiotic persists, and this allows nosocomial infections with limited options for adequate antimicrobial treatment (15). "Old" cephalosporins (e.g., ceftriaxone,

cefepime, ceftazidime) are commonly used agents in the treatment of different bacterial infections, including lower respiratory tract infections (LRTIs), thanks to their broad-spectrum activity, well-characterized pharmacological properties and low rate of adverse events (16). The overcoming prevalence of extended-spectrum β-lactamases (ESBLs), carbapenemases producing *Enterobacteriaceae* (CPE), chromosomal AmpC β-lactamases makes these drugs ineffective to treat these infections. Furthermore, the emergence of multi-drug resistant (MDR) Gram-positive bacteria such as methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant coagulase-negative *Staphylococci* (MR-CoNS), penicillin- and ceftriaxone-resistant *S. pneumoniae* (PRP and CRP respectively) and resistant *Enterococci* makes the management and treatment of these isolates challenging (17,18). Pushed by the need of new antimicrobial agents, cephalosporins had been through significant changes with the introduction of new generation agents such as ceftobiprole (19,20) and ceftaroline (21,22), ceftolozane/tazobactam (C/T) (23) or ceftazidime/avibactam (C/A) (24). Several studies have highlighted the non-inferiority of the new cephalosporins regarding their comparators (19-23,25,26). Fundamental strengths of these contemporary cephalosporins include an attractive spectrum of activity against MDR bacteria combined with high pulmonary penetration, proven harmlessness, and in some case, avoid combined therapy (15). We aimed to review the role and place in therapy of new cephalosporins in CAP and hospital-acquired pneumonia (HAP) in the setting of IMWs.

Epidemiology of pneumonia in internal medicine

The burden of Gram-positive in pneumonia is central (27), and *Streptococcus pneumoniae* is the most common bacteria causing CAP. Furthermore, approximately 16% of nosocomial types of pneumonia are a consequence of *S. aureus* infection (24). There is a close connection between influenza A virus disease and the subsequent or concurrent *S. aureus* infection: influenza A virus may increase the adhesion of *S. aureus* to respiratory tract cells boosts its proteases and simultaneously enhancing viral replication (28). For the above reasons, nasal carriers of *S. aureus*, which include from 20% to 83.7% of the general population, are at high-risk for secondary staphylococcal-pneumonia following influenza A (28).

Pneumonia due to Gram-negative bacteria (GNB), notably *Enterobacteriaceae* and *Pseudomonas aeruginosa* (PA), constitutes approximately 2% of cases of CAP, despite the increment in special populations such as older adults and high comorbid subjects (29,30). Furthermore, resistant strains are rising; notably, PA and MRSA that were reported in about 6% of CAP (31,32). As a matter of fact, according to current suggested treatments for CAP, MRSA and PA are two of the major disease-causing that would not be covered adequately with the existing strategies (29-32). Regarding HAP *Enterobacteriaceae* (e.g., *Klebsiella spp*., *Enterobacter spp*., and *Serratia spp*.), PA, and *Acinetobacter baumannii*, need to be considered (33-35). ESBL-producing *Enterobacteriaceae* and CPE related pneumonia remain a rare event in IMWs, especially in patients without prior known colonization (36-38). To systematically treat pneumonia, should be individualized the therapy considering local antimicrobial resistance and epidemiology, the stage of the illness and potential host factors predisposing to a high risk for specific pathogens (33-35).

Overview on new cephalosporins in the treatment of pneumonia in IMWs

Ceftolozane-tazobactam

This new cephalosporin combines in itself an innovative anti-pseudomonal cephalosporin, ceftolozane, albeit with pronounced similarity to ceftazidime structure, and the renowned β-lactamase inhibitor tazobactam (26). C/T, already approved for complicated urinary tract infections(cUTI) (38) and complicated intra-abdominal infection (cIAI) (39) at a dose of 1.5 g (i.e., with the ratio of 1:0.5, respectively ceftolozane and tazobactam, every 8 h) has recently been approved, to twice the previous reported daily dose, in the phase III study ASPECT-NP (23), for treatment of NP, by the U.S. Food and Drug Administration (FDA) (40) and European Medicines Agency (EMA) (41).

Antimicrobial properties of C/T

C/T is active *in vitro* against many important GNB, including multidrug- (MDR) or extensively drug- (XDR) resistant *Pseudomonas* spp. and ESBLs *Enterobacteriaceae* (42,43). As evidence of it, Farrell *et al.* have reported that C/T is the most active agent against PA (44) confirmed in several studies against strains grown in biofilms (45,46).

Ceftolozane showed an elevated activity toward the essential penicillin binding proteins (PBPs; e.g., PBP1b, PBP1c, PBP2 and PBP3) of PA (47-50) and more stability against the chromosomal AmpC β-lactamase of PA and less

reliance from its efflux pumps (e.g., Mex) or entry porins (e.g., OprD) (51,52) compared to ceftazidime.

Data from the surveillance network by Zilberberg *et al.* have shown that 22% of PA isolates from pneumonia are MDR (53) similar to those reported by Sader *et al.* (54) from the INFORM study. Moreover, INFORM study showed a rates of XDR PA among low respiratory isolates from 9.0% to 11.2% (54). In a multicenter evaluation C/T has retained its sensitivity (55) against the 36% of meropenem non-susceptible PA strains examined. Furthermore, according to Humphries *et al.* among isolates resistant to all traditional antipseudomonal beta-lactams, 52.4% were susceptible to C/T and whereas 36.4% of C/A-resistant isolates were susceptible to C/T (56). Pogue and colleagues (57) have recently compared C/T to polymyxin or aminoglycosides-based regimens supporting the preferential use of C/T to treat NP due to the more favourable clinical cure, renal profile and comparable mortality rate (57-61).

Clinical trials for C/T in pneumonia

In the ASPECT-NP trial (23), a randomized, controlled, double-blind, phase III non-inferiority trial, C/T (2 g ceftolozane and 1 g tazobactam every 8 h) was compared to meropenem (1 g every 8 h) to assess efficacy and safety in treating GNB-related NP with antimicrobial regimens lasting eight to 14 days. Clinicians from 263 hospitals in 34 countries have enrolled 726 patients, over 18 years old, subject to mechanical ventilation (MV) and randomized (1:1) to the C/T or meropenem group: the main focus of treatment was ventilator-associated pneumonia (VAP) which counted the 71% (N=519) of infections and 207 subjects (29%) had a diagnosis of HAP or ventilated-HAP (23). The first goal was to evaluate all-cause mortality at day 28 in the intention to treat population (ITT): C/T was non-inferior to meropenem in terms of both 28-day all-cause mortality [N=87 (24%) and N=82 (25.3%) respectively; weighted treatment difference 1.1% (95% CI: –5.1% to 7.4%)]. These findings were confirmed in clinical cure at test-of-cure (TOC) [N=197 (54%) and N=194 (53%) in the C/T and meropenem groups, respectively; weighted treatment difference 1.1% (95% CI: –6.2% to 8.3%)] (23). Thus, outcomes have supported the role of C/T as an alternative to carbapenems-based regimens. There was a trend toward higher rates of adverse events in the C/T compared to meropenem group (42% *vs.* 36%) but the study did not have enough statistical power to detect clearly this difference (23). Further phase IV studies aimed at assess the risk-benefit profile of C/T with careful observation and surveillance in the clinical practice are needed (62).

Lung penetration of C/T

Lung penetration of C/T has been evaluated in two phases I trials. A standard dose of C/T (e.g., 1.5 g every 8 h) has proved to be successful in reaching pharmacokinetic (PK)/pharmacodynamic (PD) target in epithelial lining fluid (ELF) in healthy individuals, for pathogens with minimum inhibitory concentration (MIC) within current susceptibility breakpoint of up to four milligrams per litre (63,64). In the ASPECT-NP trial (23), the 3 g dose was tailored for achieving maximum antibacterial activity in the lungs, even against GNB showing a MIC higher than of 8 μg/L (62,65). In healthy individuals, pulmonary the dose of 3 g every 8 h can reach ELF concentrations of >8 mg/L for 40% of the treating period and 4 mg/L for 50% of the treating period in the nearly overall of patients (62,65). Ceftolozane seemed to practically clear (92%) as an unaffected component by the renal route (40-42). Despite the reduction of dosages in patients with impaired renal function, C/T schedule for pneumonia remains loyal to time-driven PK, maintaining time between doses unchanged (q8 hours) (23,62).

Place in therapy of C/T within IMW

Different researches have studied risk factor for rectal colonization by ESBL such as advanced age, multiple medical conditions (e.g., recurrent UTIs, obstructive UTIs, diabetes mellitus, Charlson index score >3), prior past hospitalizations, recent antibiotic therapy (particularly third-generation cephalosporins and fluoroquinolones) and trips to highly endemic countries (e.g., Eastern Mediterranean countries, South-East Asia) (66-68). The overuse of carbapenems due to their efficacy against ESBL isolates resulted has helped to increased drug resistance. C/T has been proposed as part of carbapenem-sparing strategies (*Table 1*) (70). Moreover, it is known that PA is a not uncommon cause of severe pneumonia, especially in patients with chronic obstructive pulmonary diseases (COPD), bronchiectasis or former smokers, with a high mortality rate (29-32,71). C/T may be an actual and future option as "backbone" of the anti-pseudomonal regimens, flanked by a second agent, such as aminoglycoside, fosfomycin, colistin or according to the local epidemiology, a fluoroquinolone (70,72).

Ceftobiprole

Ceftobiprole medocaril, a fifth-generation, extended-

Table 1 Possible place in therapy of new cephalosporins within guidelines for the management of pneumonia

Gram-positive antibiotics with MRSA activity
Glycopeptides
Vancomycin
Oxazolidinones
Linezolid
New cephalosporins
Ceftobiprole
Ceftaroline
Gram-negative antibiotics with antipseudomonal activity: β-lactam-based agents
Antipseudomonal penicillins
Piperacillin/tazobactam
Cephalosporins
Cefepime
Ceftazidime
New cephalosporins
Ceftolozane/tazobactam
Ceftazidime/avibactam
Carbapenems
Meropenem
Imipenem
Monobactams
Aztreonam
Gram-negative antibiotics with antipseudomonal activity: non-β-lactam-based agents
Fluroquinolones
Ciprofloxacin
Levofloxacin
Aminoglycosides
Amikacin
Gentamicin
Tobramycin
Polymyxins
Colistin
Polymyxin B

Adapted from Kalil *et al.* (69). MRSA, methicillin-resistant *Staphylococcus aureus*.

spectrum cephalosporin, was currently endorsed in key European countries for the management of adult CAP (19), non-ventilator associated HAP (20) and for SSTIs, including diabetic foot (73).

Antimicrobial properties of ceftobiprole

Cell wall synthesis can be inhibited by ceftobiprole, due to its tight bindings to some PBPs of Gram-positive and Gram-negative pathogens (74). Furthermore, ceftobiprole can also interfere with β-lactams-resistant or poorly susceptible PBPs, including PBP2A of MRSA and MR-CoNS or PBP2x typical in PRP and CRP strains (74-76).

Concerning β-lactamases, ceftobiprole was recalcitrant to lytic activity by the PC1 staphylococcal penicillinase, to the class A (TEM-1 β-lactamase, SHV and K1 β-lactamase of Klebsiella oxytoca), and the chromosomal AmpC-type β-lactamases of Enterobacteriales and PA, but labile to hydrolysis by class B, class D enzymes and by class A ESBLs (77,78).

Ceftobiprole displays high efficacy against several Gram-positive pathogens including methicillin-susceptible *S. aureus* (MSSA) and MRSA also for strains with a reduced susceptibility to linezolid, daptomycin or vancomycin and against Gram-negative pathogens, including PA and not-ESBL-producing *Enterobacteriaceae* (74,79,80).

Results from a 5-year antibiotic surveillance program in Europe on ceftobiprole (SENTRY, 2005–2010), have demonstrated high effectiveness against some of the leading cause of CAP, with 99.3% (N=4,443) *S. pneumoniae* isolates testing susceptible and promising results in both *Haemophilus influenzae* and *Moraxella catarrhalis* (81).

In the surveillance study TRUST, ceftobiprole was defined as one of the most effective cephalosporins investigated and systematically accredited in clinical review literature against *S. pneumoniae* with MIC50 and MIC90 two-fold lower than ceftriaxone (82).

Nevertheless, it is a potent bactericidal agent against MRSA that sets ceftobiprole at a distance from other cephalosporins (83-88). In the time-kill analysis, ceftobiprole was bactericidal against community-induced as well as nosocomial MRSA strains (83-88).

In the SENTRY study (81), 26.9% of *S. aureus* clinical isolates were MRSA, and 98.3% of these strains were susceptible to ceftobiprole, also in strains resistant *in vitro* to linezolid, vancomycin, and daptomycin: efficacy on linezolid-resistant MRSA was also confirmed by the CLASS study, assessing the *in vitro* action of ceftobiprole, issued by

Rossolini *et al.* across 19 countries (86).

Furthermore, ceftobiprole, disclosed action against PA (64.6% disposed of by the EUCAST-specific susceptibility breakpoint of 4 μg/mL) that was less than cefepime (78.6% susceptible) and ceftazidime (75.4% susceptible) (81,89-91).

Clinical trials for ceftobiprole in pneumonia

Two phase III trials demonstrated the efficacy and safety of ceftobiprole (19-20). The first one was a non-inferiority, double-blinded, multicentre, randomised study in 638 patients hospitalised for the treatment of severe CAP (19). The authors, compared ceftobiprole medocaril (500 mg/8 h) with ceftriaxone (2 g/day) with optional linezolid (600 mg/12 h)-when MRSA or ceftriaxone-resistant *S. pneumoniae* was thought to be involved (19).

Ceftobiprole was found not inferior to ceftriaxone, whether as monotherapy or combined with linezolid (19).

Awad and colleagues (20) in a double-blinded, multicentre randomized study comparing ceftobiprole medocaril to ceftazidime and linezolid in 781 patients treated for HAP and VAP showing non-inferiority against comparators, with the exception of patients with VAP (20).

Possible explanations for these results are the insufficient sample size, a substantial conglomeration of baseline clinical features and appreciable heterogeneity in the VAP subgroup. Besides, another critical statistical difference was perceived in the subgroup of subjects with microbiological evidence of MRSA infection (94.7% in the ceftobiprole group *vs.* 52.6% in the ceftazidime plus linezolid group [difference, 42.1 (95% CI: 17.5–66.7)]. For the secondary effectiveness criteria, the microbiological eradication rates at the end of management visit in patients with HAP were comparable in the ceftobiprole and ceftazidime/linezolid groups (20). Interestingly, in patients with HAP requiring MV for less than 48 h, clinical outcomes were in favour of ceftobiprole (20,92,93).

Lung penetration of ceftobiprole

ELF concentrations of ceftobiprole were assessed in fit subjects at steady-state: mean ceftobiprole concentrations in the ELF were lower than in the plasma (94,95). Population PK demonstrating grounded on these data showed that average dissemination into the ELF was 25.5% (interquartile range, 7.9–30.4%) (95-97). In the murine model of pneumonia (95), lung penetration of ceftobiprole, based on AUC values in the ELF and plasma, was more elevated (median 68.8%) than in healthy individuals. However, the calculated ELF levels of antibiotics may barely predict β-lactam concentrations at the site of infection (96), specifically in studies in healthy volunteers. A review of clinical studies examining the ELF concentrations of ceftobiprole with those of other cephalosporins displays that lung penetration with the bulk agents was similar to that observed with ceftobiprole (94,97).

Place in therapy of ceftobiprole within IMW

Ceftobiprole may be a good option in severe CAP leading to complications associated with influenza, in which practical coverage of community-associated MRSA (CA-MRSA) should be guaranteed (*Figure 1*) (92) especially in patients with diabetes, obese, COPD or patients with lung abnormalities, patients older than 65 years or patients with underlying malignancies (92,93,98). Scheeren *et al.* (98), in a post-hoc analysis from the two phase III trials (19-20), evaluated the consequences in a smaller group of high risk subjects with community induced or NP and they showed advantages of ceftobiprole compared to other medications in terms of premature progress in the recovery for high-risk patients, and in high-risk HAP and patients with up to ten underlying comorbidities at baseline (98). Thanks to its safety and efficacy also in frail population, ceftobiprole should be considered in severe pneumonia and in patients at high risk of mortality (92-94,98,99). Ceftobiprole might be useful also in post-obstructive pneumonia, a clinical entity due to an infection of the lung parenchyma distal to the bronchial obstruction in lung cancer patients, notably to endobronchial or extraluminal obstruction due to cancer growth (100). Post-obstructive pneumonia presented a polymicrobial flora predominantly with the high rate of gram-positive pathogens, including MRSA: ceftobiprole monotherapy due to its safety may guarantee a low risk of an adverse event in this frail population (100).

Guidelines for NP (69,101) demand rapid empiric antimicrobial regimens using a combination of antibiotics grounded in local patterns and patient risk factors. Furthermore, initial empirical monotherapy might be used whenever possible to decrease the risk of MDR growth (70,102). Ceftobiprole combines an excellent spectrum for pathogens involved in HAP, with low risk and low rate of MDR GNB, in frail patients admitted to the hospital at high risk of adverse events caused by non-β-lactam anti-MRSA-agents as well as MRSA infection. Alongside qualities above mentioned, ceftobiprole reports a minimal risk in the selection of resistant mutants in Gram-positive or GNB and no significant impact on the healthy human intestinal flora (92-94).

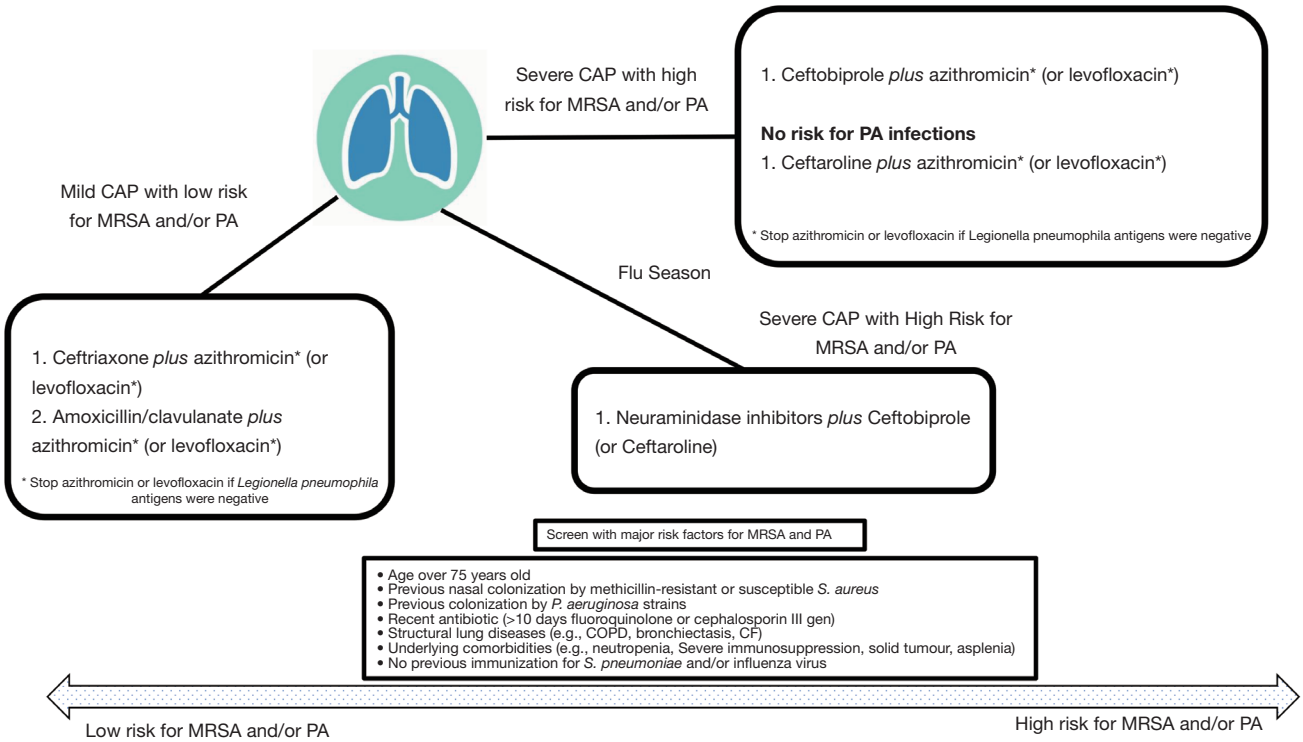

Figure 1 Place in therapy of ceftobiprole and ceftaroline in community-acquired pneumonia. CAP, community-acquired pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; PA, Pseudomonas aeruginosa; COPD, chronic obstructive pulmonary disease; CF, cystic fibrosis.

C/A

C/A is an intravenously third-generation cephalosporin (i.e., ceftazidime) with the non-β-lactam β-lactamase inhibitor avibactam (103). C/A was previously validated for cIAI (104) and cUTI (105) therapy and has demonstrated activity against common GNB even with the expression of clinically relevant class A, C and some D Ambler's β-lactamases or *Enterobacteriaceae*-producing chromosomal AmpC, ESBLs, and OXA-48 enzymes (103).

Antimicrobial properties of C/A

Ceftazidime is primarily an inhibitor of PBP3: adhering to PBPs, thereby causing the defects in cell wall formation with a binding affinity that vary between cephalosporins (106). On the other hand, avibactam inactivates susceptible β-lactamases by serine-residue covalent acylation: avibactam, through *in vitro* studies, has shown an attractive activity *vs.* Ambler class A [e.g., ESBL and Klebsiella pneumoniae carbapenemase (KPC)], class C (e.g., AmpC), and some class D (e.g., OXA-48) enzymes (107,108).

This new combined-cephalosporin offers an exceptional action to ESBL- and AmpC-producing *Enterobacteriaceae* comprising strains that allow the of both enzymes (109-112). This activity was confirmed in samples collected in studies from U.S. (113,114) and European (115) countries. One of the largest database, the INFORM (International Network For Optimal Resistance Monitoring) global surveillance study (116), has counted 34,062 isolates of *Enterobacteriaceae* from multiple sites and infections (e.g., IAI, UTI, SSTI, LRTI and bloodstream infections) in 176 medical centre laboratories from 39 countries): 99.5% of *Enterobacteriaceae* isolates were susceptible to C/A with a MIC ≤8 μg/mL (defined resistant to MIC ≥16 μg/mL) (115). Lately, it was designated as inhibitory mechanism rooted on a mutation of an AmpC alternate by removal of single amino acid and a lower affinity to C/A in some *Enterobacteriaceae* cloacae extended-spectrum AmpC (ESAC) β-lactamase enzymes (116-118): despite that resistance due to AmpC variant has remained anecdotal.

C/A has shown *in vitro* susceptibility rate up to 98% against KPC-producing *K. pneumoniae* isolates from most

U.S. and European hospitals (119-123). Although only a few studies have differentiated activity of C/A against KPC subtypes, emerging data indicate that KPC-3-producing strains have higher MICs than KPC-2 producers (124,125). C/A-resistant strains among KPC-producing *Enterobacteriaceae* may appear due to mutations that increase ceftazidimase specificity rather than conferring avibactam resistance; nevertheless, its current medical significance remains undefined (119-123).

While in the year 2015, the first report on of C/A resistance in a KPC-3-generating *K. pneumoniae* was reported (123), and additional cases have been defined ever since (124,125). Therefore, despite being a favourable remedy, C/A use should be cautious (126). For GNB, it has activity against strains generating class D carbapenemases as OXA-24 and OXA-48 (127), as well as OXA-40 and OXA-69 (128). Among PA strains, an examination of 3,902 aggregates from 75 U.S. clinical centres recognised that 96.9% of the strains were receptive to C/A (MIC ≤8 μg/mL) (129). In the same survey, susceptibility to C/A for MDR and XDR Pseudomonas strains was 81.0% and 73.7%, respectively. In 2017, the same authors assessed 7,686 isolates from the same hospitals, confirming previous results (114). C/A has been compared with C/T against PA with similar susceptibility percentages, but lower MIC for C/T (55,114,130,131).

Clinical trials for C/A in pneumonia

C/A has previously proven its clinical efficacy for the treatment of severe GNB infections in phase III trials of cIAI and cUTI, receiving approval in both in the U.S. as well as in the European countries (104,105). Recently in a phase III, randomized, double-blind, double-dummy trial, the REPROVE study, investigators have proved the non-inferiority of C/A *vs.* meropenem in hospitalized adults with HAP/VAP due to GNB, including ceftazidime non-susceptible strains (C/A-NS) (25). Eligible patients, recruited for 24 countries, included hospitalized adults (aged 18–90 years) randomized 1:1 to receive either C/A 2.5 g (2.0 g ceftazidime plus 0.5 g avibactam, q8h IV over 2 h) plus meropenem placebo or meropenem 1 g (q8h IV over 30 minutes) plus C/A placebo for 7 to 14 days (25). Additionally, from randomization, open-label aminoglycosides, and linezolid or vancomycin were permitted while awaiting culture results for 24 to 72 h (25,132-134). The primary endpoint in this study was clinical cure at the TOC visit with additional secondary endpoints, including all-cause 28-day mortality (25). In the ITT group, 69% of subjects in the C/A group were clinically treated at the TOC stay when compared to 73% in the meropenem group. At the same instance, 77% in the C/A group and 78% in the meropenem group attained medical therapy in the sample population (25). All-cause fatality rates seemed to be 8% and 7% in the C/A and meropenem groups, respectively (25). This registration study has also placed some dubiousness about safety in the C/A group compared to meropenem, with reported higher rates of serious adverse reactions (19% *vs.* 13%) and adverse events leading to study drug discontinuation (4% *vs.* 2.7%) (132-134).

Lung penetration of C/A

From both, PK and PD modelling studies have resulted that C/A at the standard dose (2.5 g every 8 h) infused over 2 h, reached ELF's favourable concentrations (135). Analysis using a population PK model found that the proportion of the medicating interval that the free-drug absorption of C/A rests above the MIC (%fT>MIC) that is essential in leading to a favourable result in subjects with HAP was >45% (135,136). Preclinical results in rats indicated that permeation of the medication in the lung is about 30% of the plasma absorption and PK/PD studies in individuals established the validity of preclinical data in animals (135-139). In terms of PK, the lung' penetration of C/A is just about 25–35% of the absorption in the plasma and was assessed in two phases I studies (135,136). ELF penetration of C/A is minor when compared to piperacillin (40–50%) or meropenem (50%) (136).

Place in therapy of C/A within IMW

Data from the REPROVE study (25,132) have defined C/A as a valid alternative to carbapenems in carbapenem-resistant Enterobacteriaceae (CRE) nosocomial respiratory infections. Despite that, should be considered that patients in the clinical practice who are receiving C/A, might be frail, with several comorbidities (133,134). De novo resistance and development of resistance during C/A therapy, are reported in literature (123-126). These reports increase the likelihood of a relatively low barrier to resistance for C/A and have important implications for antibiotic stewardship programs (123-126). Shields *et al.* (140) evaluated risk factors associated with C/A failures and the development of resistance in a cohort of adults (n=77). Most failures have occurred in the pneumonia group (64%), compared to patients with urinary tract infections and blood-stream infections who experienced

higher success rates (88% and 75%, respectively). Alongside pneumonia, renal replacement therapy was defined as independent predictors of clinical failures (140). Assuming the potential advantage of this new cephalosporin to treat CPE infections, discretion should be implemented to bound the extensive use of C/A for culture-negative infections or when more narrow-spectrum antibiotics are still active (141). C/A with its broad activity against ESBLs and chromosomal Amp-producing *Enterobacteriaceae* may be a practical choice to spare carbapenems in these fields (*Table 1*). Despite the placing on the market of C/T, C/A should not be forgotten in the management of PA pneumonia (142,143). Furthermore, clinical studies with C/A in MDR/XDR PA infections are scarce and contain low numbers of patients: the cure rates were close to 80%, and most failures occurred in respiratory tract infections (144,145).

Ceftaroline

Ceftaroline is a novel generation cephalosporin distinguished by a particular spectrum of activity on common bacterial causes of CAP (21,22). In the US, because of failure of the approval of ceftobiprole for CAP, is at the moment the only anti-MRSA cephalosporins available for LRTIs (146).

Antimicrobial properties of ceftaroline

Ceftaroline spreads its antimicrobial activity by specifically binding of PBPs, notably to the PBP2a, an MRSA-specific protein that has low affinity for most other β-lactam antibacterials (147).

Among *Staphylococcus spp*. strains, by comparing ceftaroline and ceftriaxone, the first has resulted more potent in both instances, against MSSA (≥16-fold) and MRSA (≥32-fold) (148).

Moreover, susceptibility rates for ceftaroline against MRSA isolates were reported broadly high (between 68.2% to 93.6%) but changeable between states and regions, with a more favourable profile in European than in Asian or South American countries (149-154).

Ceftaroline also retains an attractive spectrum of activity on other Gram-positive bacteria, notably vancomycin-intermediate *Staphylococcus aureus* (VISA), heterogeneous VISA (hVISA), vancomycin-resistant *Staphylococcus aureus* (VRSA) or daptomycin non-susceptible *S. aureus*, linezolid-resistant *S. aureus*, MR-CoNS and Streptococci, including MDR *S. pneumoniae* (149-152).

Among *S. pneumoniae* strains, ceftaroline was comparable to ceftriaxone in the treatment of penicillin-susceptible strains but more effective in a subject infected by MDR *S. pneumoniae* strains (150-153). Ceftaroline susceptibility in the AWARE program among penicillin-resistant Streptococcus pneumoniae ranged from 77.4% to 100% (154)

Ceftaroline also exhibits potent *in vitro* activity against GNB, including *Haemophilus spp*., *Moraxella catarrhalis*, *Morganella morganii* and not-ESBL or AmpC-producing *Enterobacteriaceae* (150-153).

Clinical trials for ceftaroline in pneumonia

Ceftaroline was approved for the treatment of CAP according to FOCUS 1 & 2 studies, two phases III randomized controlled trials (RCTs) (21,22). Both studies were conducted in an adult population with radiologically confirmed moderate-to-severe CAP comparing ceftaroline (600 mg q12h) *vs*. ceftriaxone (1 g q24h), with an additionally empiric macrolide (on day 1) within-subjects enrolled in FOCUS 1, for atypical pathogen coverage. Subsequently, in Asian subjects was performed, a phase III, non-inferiority with nested superiority trial, using ceftriaxone 2 g q24h as a comparator (155). Of note, in all these studies patients with a definite diagnosis of MRSA or high-risk subjects for MRSA infection were excluded, owing to the inactivity of ceftriaxone against these strains (155).

In both FOCUS 1 & 2 (21,22), ceftaroline showed a proper safety and efficacy, achieving non-inferiority to the comparator in the co-primary modified ITT efficacy and clinically evaluable populations for the primary endpoint of clinical cure at the TOC visit. In the unified examination of FOCUS 1 and FOCUS 2, clinical cure rates for patients with MSSA CAP at the TOC appointment in the microbiological reformed ITT efficiency inhabitants were 72% (18 of 25) with ceftaroline fosamil, related with 60% (18 of 30) for ceftriaxone (21,22,155). With ceftaroline, the clinical cure was achieved in up to 80% of cases and was still associated with a shorter time to clinical response than ceftriaxone.

The combined examination of FOCUS 1 and FOCUS 2 providing a well-being data set of 1,228 patients, with ceftaroline fosamil representing an encouraging well-being and tolerability profile, as predictable for a cephalosporin, with similar rates of adverse events for ceftaroline fosamil (47.0%) and ceftriaxone (45.7%) (21,22,155).

Lung penetration of ceftaroline

ELF penetration of ceftaroline was assessed in a phase I study among fifty-three healthy subjects at different

dosing (600 mg, bid and 600 mg, tid) for which free lung ceftaroline was approximatively 23% (22.5% and 23.6%, respectively in the groups) and analogous to other β-lactams (156). In a staphylococcal murine pneumonia model, Riccobene *et al.* have demonstrated that absorption of ceftaroline in ELF in a human model was comparable to serum absorption, causing in similar fT>MIC values in serum and ELF: the dissemination of free ceftaroline into ELF, was 23% (156). Furthermore, they have reported that ceftaroline promptly infiltrating into ELF with maximum concentrations occurring at the end of infusion (156).

Employing plasma and ELF exposure data, stimulated that were evaluated to achieve fT>MIC goals of 42.0% for plasma and 17.0% for ELF (156-158) in a staphylococcal murine-pneumonia model. For ceftaroline 600 mg q12h, 98.1% of counterfeit patients acquired a 42.0% fT >1 mg/L in plasma, and 81.7% also attained a 17.0% fT >1 mg/L in ELF (156,157). For ceftaroline fosamil 600 mg q8h, 100% and 94.7% of simulated patients achieved the respective plasma and ELF targets (156-158).

Place in therapy of ceftaroline within IMWs

Ceftaroline unites in itself a high bactericidal activity against a wide spectrum of pathogens involved in pneumonia (149-151) with a favourable posology: 5 to 7 days of twice-a-day administration schedule is recommended in patients with CAP (21,22,152). Ecological impact of ceftaroline on gut and microbiota is less known, theoretically minimal due to low faecal excretion. Differences in metabolism and excretion, have identified ceftaroline as a good alternative in patients who complain a biliary tract disease with at risk for pseudo-cholelithiasis. Ceftaroline is a desirable option in a patient admitted for CAP, with high risk for MRSA or previously known colonization and haematologic features of chronic anaemia or low platelets, in which treatment with a valid molecule such linezolid may increase the risk of bone marrow hyporegeneration (*Figure 1*) (15,28). Furthermore, ceftaroline is a favourable option in Staphylococcal-pneumonia, according to its higher ELF penetration than glycopeptides and low risk of nephrotoxicity. Staphylococcus-related pneumonia might be secondary to a previous or current bacteremia, as reported for central venous catheter (CVC) related bloodstream infections or infectious endocarditis: involvement of the lungs, as multifocal pneumonia spreading from septic embolism, could be in the presence of specific interest of this extended-spectrum cephalosporin (15,28,159,160).

Ceftaroline as for ceftobiprole may be first-line agents, flanked by neuraminidase inhibitors, in severe CAP complicating influenza for their known anti-MRSA activity (*Figure 1*) (15,28,159-162).

Conclusions

The arrival of new cephalosporins has helped to reach some niche populations, otherwise difficult to access (e.g., post-flu pneumonia, PA pneumonia, CRE pneumonia) and to give valid alternatives to the previously known antibiotics in this field. Ceftobiprole and ceftaroline provide valuable benefits against MRSA and MDR *S. pneumoniae* avoiding combination, flanked by a stimulating spectrum on GNB (including PA for ceftobiprole). Furthermore, ceftobiprole and ceftaroline may guarantee a low rate of adverse events and very restricted drug-to-drug interactions during treatment of LRTIs, also in frail patients. C/T and C/A are a useful weapon in pneumonia due to MDR PA, CRE and ESBL-producing *Enterobacteriaceae*. C/T and C/A are valid alternatives to spare carbapenems, notably when carbapenems are not well tolerated, in empiric and targeted treatments in this field.

Pivotal in the use of this new cephalosporins is to describe and define better the features of the patient by assessing the risk of MRSA or MDR GNB colonization, underlying lung abnormalities or systemic diseases, the grade of severity of pneumonia, risk of adverse events or drug-related toxicity. In other words, currently, the approach to pneumonia infection must be targeted to the individual based on the clinical situation, the intrinsic host characteristic, the susceptibility profile, and local epidemiology and the "universal pneumonia antibiotic strategy" is no longer acceptable for treating lung infections.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/jtd-20-417). FGDR and SC were speaker for Pfizer, MSD and Correvio, FGDR was part of advisory board for Pfizer, MSD. The other authors have no conflicts of interest to declare.

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