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Safety and Effectiveness of Fifth Generation Cephalosporins for the Treatment of Methicillin-Resistant Staphylococcus aureus Bloodstream Infections: a Narrative Review Exploring Past, Present and Future

ABSTRACT

Introduction: Methicillin-resistant *Staphylococcus aureus* (MRSA) bloodstream infections (BSIs) is a major issue in healthcare, since it is often associated with endocarditis or deep site foci. Relevant morbidity and mortality associated with MRSA-BSIs forced the development of new antibiotic strategies; in particular, this review will focus the attention on fifth generation cephalosporins (ceftaroline/ceftobiprole), that are the only ß-lactams active against MRSA.

Areas covered: The review discusses the available randomized controlled trials and real-world observational studies conducted on safety and effectiveness of ceftaroline/ceftobiprole for the treatment of MRSA-BSIs. Finally, a proposal of MRSA-BSI treatment flowchart, based on fifth generation cephalosporins, is described.

Expert opinion: The use of anti-MRSA cephalosporins is an acceptable choice either in monotherapy or combination therapy for the treatment of MRSA-BSIs due to their relevant effectiveness and safety. Particularly, their use may be advisable in combination therapy in case of severe infections (including endocarditis or persistent bacteriemia) or in monotherapy in subjects at higher risk of drugs-induced toxicity with older regimens. On the contrary, caution should be used in case of suspected/ascertained central nervous system infections due to inconsistent data regarding penetration of these drugs in cerebrospinal fluid and brain tissues.

KEYWORDS: Fifth generation cephalosporins; Ceftaroline; Ceftobiprole; Staphylococcus aureus; Methicillin-resistance; MRSA; bloodstream infections.

1. Staphylococcus aureus bloodstream infections: the state of art

1.1. Epidemiology and microbiology of Staphylococcus aureus

S. aureus was discovered in the 1880s, in a time when infection by this bacterium claimed the life of the 80% of affected individuals [1]. The introduction of penicillin in medical use in 1940, brought about a radical but fleeting change in the prognosis of *S. aureus* infections. Already in 1942, in fact, the first penicillin-resistant *S. aureus* isolate was observed in a hospital, and shortly after in the community. By 1960, the rate of penicillin resistance by acquired β-lactamase enzymes had risen to 80%, and methicillin (a penicillinase-resistant penicillin) was introduced in clinical use. But, again, success was ephemeral. In just a couple of years, *S. aureus* developed methicillin-resistance thanks to the acquisition of a large mobile genetic element known as the staphylococcal chromosome cassette *mec* (SCC*mec*), becoming the world-renowned methicillin-resistant *S. aureus* (MRSA). Even today, after decades of research and innovations, MRSA is one of the top pathogens *"that keeps clinical infection specialists up at night*", in virtue of its nearly pan-β-lactam resistance profile and association with significant mortality [2].

1.2. General epidemiological features of S. aureus

Staphylococci are ubiquitous gram-positive cocci adapted to be common human commensals on the skin and mucous membranes. All of them have evolved to survive in these harsh environments, being able to tolerate aerobic and anaerobic atmosphere, the presence of a high concentration of salt, and temperatures ranging from 18°C to 40°C. What makes *S. aureus* unique compared to other species of the *Staphylococcus* family (e.g. coagulase-negative staphylococci), is the expression of additional virulence determinants that promote tissue colonization, invasion, escape to phagocytosis and tissue damage by toxins production [3].

Besides being a common cause of skin, soft tissue and bone infections, *S. aureus* is a leading causes of nosocomial infections, that ranges from surgical site infections (SSIs) - in particular general, orthopedic, cardiac, and neurosurgeries [4,5], to pneumonia, bloodstream infections and sepsis in nonsurgical patients – including dialysis patients, HIV-infected patients and patients in intensive care units (ICUs) – [6-9]. In 2019, the European Centre for Disease Prevention and Control (ECDC) reported that the 18.7% of ICU-acquired pneumonia episodes, the 11.1% of ICU-acquired bloodstream infections (BSIs), and the 15.2% of SSIs in Europe were attributable to *S. aureus* [5,10].

Nasal colonization is a major risk factor for the development of invasive staphylococcal infections [6,11], and constitute the reservoir for the spread of the pathogen in the population [3]. Approximately 20% of adults are chronic (persistent) nasal carriers of *S. aureus*, while an additional 60% may carry the organism intermittently [3,12,13]. From the nose, the skin (and hands) can become colonized, with intermittent skin carriage rates as high as 40% [14]. The hands of colonized subjects, including health-care workers, are then the main source for *S. aureus* transmission in both household and hospital settings [15,16], along with the less-frequent possibility of airborne transmission [14]. Current estimates report that 25-30% of subjects are colonized with methicillin-sensitive *S. aureus* (MSSA), while 1-3% carry an MRSA [17,18].

1.3. Methicillin-resistant S. aureus (epidemiology, microbiology)

Ever since its emergence in the 1960s, MRSA has become an epidemic across the globe and only pathogen–drug combination able to cause more than 100,000 deaths and 3.5 million Disability Adjusted Life Years (DALYs) attributable to resistance in the world [19]. MRSA is one of the six pathogens associated with the higher burden of deaths related to drug resistance worldwide, ranking first in high-income countries [19]. There is marked geographical variation in MRSA burden, probably as a consequence of the circulation of multiple clones generated from the independent acquisition of SCCmec [20]. In Europe, the population-weighted percentage of MRSA isolates in 2021 was of 15.8% [21], and the 11.0% of ICU-acquired *S. aureus* infections were attributable to this resistant pathogen [10].

Penicillins are a class of β-lactam antibiotics that bind and inactivate penicillin-binding proteins (PBPs), critical enzymes that cross-link peptidoglycan components and strengthen the cell walls of most bacteria, including gram-positive cocci as *S. aureus*. β-lactam resistance in MRSA originates from the horizontal acquisition of SCC*mec*, followed by clonal expansion of the resistant isolates. SCC*mec* contains the *mecA* (or occasionally called *mecC*) resistance gene, coding for an alternative 78-kDa penicillin binding protein PBP2a [2]. PBP2a is able to able to substitute for the function of the other PBPs, thus preserving bacterial replication capacity in the absence of treatment. Yet, it has low affinity for all β-lactams, thereby strongly reducing clinical efficacy against MRSA. Today only two V-generation cephalosporins — ceftaroline and ceftobiprole—are efficacious against the most highly pathogenic MRSA strains [22,23].

78 *1.4. Epidemiology, morbidity, mortality and risk factors for S. aureus bloodstream infections*

79 *S. aureus* is the second most common pathogen causing bloodstream infections (BSIs) worldwide, head to
80 head with *Escherichia coli* [24], with estimated incidences of 9.3 to 65 cases/100,000 persons per year [25,26]
81 and a case-fatality rate ranging between 15 and 40% [27-30]. Even though mortality due to *S. aureus*
82 bacteremia has gradually decreased over the last 30 years [31], we still observe a huge variability in outcome
83 estimates, that reflects the heterogeneity of clinical settings and patient populations analyzed, with a significant
84 impact of age (extremities in particular), route of acquisition, site of primary clinical focus, presence or absence
85 of indwelling medical devices, pathogen characteristics, and host predisposition (e.g. Charlson co-morbidity
86 index and SOFA score at admission, intravenous drug use, low socioeconomic status) [27,32-35].
87 In recent years, substantial progress has been achieved in preventing MRSA BSIs after widespread introduction
88 of enhanced infection control efforts, including generalization of hand-washing (using hydro-alcoholic
89 solution), mirrored by a generalized decrease in the incidence of MRSA BSIs in US and Europe, as well as in
90 other countries with systematic surveillance [29,36,37]. The prevention of spreading of MRSA strains appears
91 crucial, due to the severity of infections. In particular, community acquired MRSA strains may harbors genes
92 for Panton Valentine leucocidin (PVL); the expression of PVL toxin may cause more severe and complicated
93 kin and soft tissue infection infections and pneumonia. This characteristic lead to an increase of morbidity and
94 mortality for community acquired MRSA, if compared to hospital acquired MRSA and MSSA infections [38].
95 As for other invasive infections, persistent nasal carriage is an important risk factor for *S. aureus* BSIs, and as
96 high as 80% of *S. aureus* blood isolates in bacteremia events are of endogenous origins, identical to those
97 isolated from the anterior nares of corresponding patients [6,11]. Entryways for *S. aureus* bacteremia can be
98 multiple, and eventually remains undetermined in up to 25% of cases. Yet, several cohort studies agreed in
99 identify contaminated indwelling devices (e.g. intravascular catheters and implantable medical devices),
100 SSTIs, pleuropulmonary and osteoarticular infections as main sources for *S. aureus* bacteremia [34,39].
101 Once in the bloodstream, *S. aureus* can seed and establish metastatic infections in virtually any body site,
102 ensuing complications that may result in significant morbidity and mortality. Metastatic complications,
103 anatomically unrelated to the primary site infection, occur at rates that range from 11% to 53% [35] and include
104 osteomyelitis, deep-seated abscess, septic arthritis and infective endocarditis [40]. Some of them frequently
105 require ICU admission, multiple diagnostic interventions, and therapeutic lines, and carry poor prognosis

because of the anatomic site or the difficulty in reaching a timely diagnosis. Notably, early infectious disease consultation (and underlying quality of care process) is one of the few modifiable factors that improves survival to *S. aureus* BSIs [41-44].

2. Current approach to Staphylococcus aureus bloodstream infections

2.1. The complexity of Staphylococcus aures bloodstream infection.

Due to the virulence mechanisms and the strong biofilm-forming ability [45], *S. aureus* BSI (SA-BSI) are frequently complicated by dissemination of the infection to prosthetic materials, on both natural and prosthetic valves (endocarditis) or on intracardiac devices (ICD), bone and joints, skin and soft tissues (creating abscesses), causing metastatic diseases [34].

Particularly, disseminated infections are more frequent in community-acquired (CA) BSI and in association with persistent bacteremia. [46,47].

According to its complexity, an infectious disease (ID) specialist consultation has become mandatory for the management of SA-BSI, in order to reduce morbidity, mortality, length of hospital stay by ensuring adherence to several pivotal treatment strategies (bundles) envisaged by current guidelines [48].

To uniform clinical management and ensure appropriateness of treatment, SA-BSI are divided in two main types, uncomplicated and complicated BSI.

The Infectious Diseases Society of America defines the “uncomplicated bacteraemia” as a bacteraemia with no evidence of IE and absence of implanted prostheses, negative follow-up blood cultures drawn two to four days after the initial set, defervescence within 72 hours after initiating appropriate antibiotic therapy, and no evidence of metastatic infection [49]. On the contrary, “complicated bacteraemia” was defined by Lopez et al. if one of the following criteria is present: persistent bacteraemia, development of endocarditis or metastatic foci, presence of Janeway lesions, Osler nodes, or other cutaneous or mucosal lesions suggestive of acute systemic infection (including petechiae, vasculitis, infarcts, ecchymoses, pustules, Roth spots, or conjunctival hemorrhage) in the absence of a firm alternate explanation, presence of any permanent prosthetic device, any device-related infection where the device could not be removed in the first 3 days, SAB in patients under chronic haemodialysis [50].

134 *2.2."Bundles-of-care" approach*

135 Since SA-BSI is often complicated and burdened by a great morbidity and mortality, numerous studies have
136 been carried out to identify risk factors of poor outcome and improve the management of these patients.
137 In 2013 Lopez-Cortes *et al.* [50] identified quality of care indicators to implement when facing a SA-BSI
138 (**Table 1**).
139 The usefulness of the adherence to these bundles has been established in several subsequent works [51-53]
140 and they are now considered a standard of care, along with an ID consultation [54].
141 In detail, these "bundles" included: follow-up blood-culture, early source control, echocardiography, and
142 appropriate antibiotic therapy according to the presence of MSSA or MRSA, in order to quickly identify
143 patients with complicated SA-BSI and provide the optimal management.
144 *Follow-up blood cultures*. The performance of follow-up blood cultures is useful to identify persistent
145 bacteremia and patients at higher risk of complications. Authors suggest performing follow-up blood cultures
146 after 48-96 h after starting of an appropriate antimicrobial therapy. The duration of SA bacteremia represents
147 a risk factor for mortality and is often associated with the presence of a deep side infection and/or poor source
148 control. Complications (risk of death, prolonged hospital stay or admission in Intensive Care Unit) significantly
149 increase after 3 days of bacteremia [50].
150 *Early source control*. It was defined as removal of non-permanent vascular catheter if suspected or confirmed
151 as the source of SA bacteraemia, or drainage of an abscess in <72 h, and represents one of the most important
152 quality indicators. In fact, the presence of an infected catheter or device, or the presence of an undrained
153 abscess are major risk factors for persistence of bacteriemia, recurrence of the infection and death [55].
154 *Echocardiography*. Transthoracic echocardiography (TTE) should be performed in all patients with SA-BSI,
155 since it is a rapid, non-invasive test, that can provide important information about the presence or not of
156 endocarditis. Trans-oesophageal echocardiography (TEE), that is more invasive and could be burdened by
157 more complications, should be reserved to patients with high risk of IE, particularly patients with community-
158 onset of SA-BSI, presence of prosthetic valves or ICD, persistent bacteraemia or disseminated infection with
159 negative TTE. In case of positive TTE, TEE should be also considered since it has a higher sensibility in case
160 of perivalvular abscesses, valve perforation and to define the dimension (and embolization risk) of the
161 vegetation. These characteristics of IE are important to give surgical indication of endocarditis [50].

Appropriate antimicrobial therapy. *S. aureus* should be considered the potential causative organism in case of sepsis and septic shock, due to the aforementioned mechanism of virulence. Since MSSA is susceptible to ß-latcams, an empirical therapy in case of sepsis and septic shock is usually effective against this pathogen, pending for blood-culture results. In addition, in case of seosis and septic shock, an anti-MRSA coverage should be considered when the patient presents risk factors for MRSA colonization, i.e. recent hospitalization, residence in long-term care facility, recent surgery, hemodialysis, prior antibiotic treatment, and high APACHE score [56]The treatment of MRSA-BSI is still a matter of debate, and the best options seems to be represented by glycopeptides, lipopeptides or new fifth generation cephalosporins. In addition, some may dispute also the usefulness of oxazolidinone such as linezolid, particularly when outpatient therapy is a valid option [57].

Duration of treatment. The appropriate duration of the treatment represents one of the bundles of the quality of care in the management of SA-BSI. The duration of the treatment is also still controversial.

In case of complicated bacteraemia, the suggested minimum duration of therapy is 28 days, but could be longer, depending on the site of infection that requires sterilization. For infective endocarditis (IE), according to different guidelines and depending on if is a native valve endocarditis (NVE) or a prosthetic valve endocarditis (PVE), a treatment of 4-8 weeks is recommended [58].

For implantable cardioverter defibrillator (ICD) infections, the treatment duration depends on the presence of endocarditis. If only the pocket is infected, 14 days of antibiotic therapy after the removal of the ICD is recommended. In case of vegetations on TTE after removal, 4-6 weeks is recommended [59].

For non-vertebral osteomyelitis a similar duration is recommended while spondylodiscitis could need longer duration of treatment [60]. Osteomyelitis should also be treated surgically in order to be completely eradicated, especially when there is a subperiosteal or soft tissue abscess, an osseous sequestrum, or other evidence of a chronic infection, like a sinus tract infection. Other indications to surgery include infections that do not respond to appropriate antibiotic therapy or concomitant septic joint arthritis [61].

Prosthetic joint infections (PJI) are difficult to manage, and duration of treatment is strongly dependant by surgical strategy adopted. Surgery represents the cornerstone of the therapy to eradicate the infection. Six weeks is the minimum recommended duration of antibiotic therapy, but no clear evidence is available [62]. Often a longer duration is needed, depending on the type of surgery performed (Debridement Antibiotics and Implant Retention (DAIR), explantation-reimplantation in 2 or 1 stage). A randomized controlled trial was

published on NEJM on 410 patients with PJI. The two groups (205 vs 205 patients) were randomly assigned to receive 6 vs 12 weeks of antibiotic course. The trial failed to show the non-inferiority of 6-weeks antibiotic course, with a higher percentage of patients with unfavourable outcomes [63].

Finally, in some cases, chronic suppressive therapy is warrantable when a prosthetic infection (PJI, PVE etc.) cannot be eradicate with surgery [64].

On the other side, after a complicated bacteraemia is excluded, the duration of antibiotic therapy should be prolonged for 14 days from the first negative follow-up blood culture, in order to reduce the risk of infection relapse [65]. In fact, a prospective observational study showed that relapse occur more frequently in patients treated < 14 days (8% vs 0%) [66]. Nevertheless, in selected low-risk patients, a shorter duration of therapy could be considered: in a retrospective cohort Danish study, 1005 patients with MSSA-BSI divided in three cohorts were treated with prolonged (714 patients) or short course (291 patients) with no association at the multivariate analysis with higher 90-d mortality and 30-d mortality in patients treated with short course [67]. Consequently, a potential short course of therapy is feasible, as suggested by other experiences [68,69], but more studies are still needed.

3. Current treatment strategies for MRSA bloodstream infections

3.1 Backbone of therapy: vancomycin, daptomycin, linezolid

Beta-lactams represent the cornerstone of the antibiotic treatment since their introduction in 1930 and have several clinical indications. Their favourable safety profile and great effectiveness against a great number of infections [70] make them the most prescribed class of antibiotics in the world, sometimes leading to unjustified abuse, with the emergence of antibiotic resistance.

For what concern MSSA infections, β-lactams had demonstrated superiority to other antibiotic classes in several studies, making cefazolin and anti-staphylococcal penicillins (ASP) the first-line therapy of choice [–71-73].

However, since the spread of MRSA strains ß-lactams resulted ineffective, posing a serious treat for the therapy of MRSA infection. In this setting, glycopeptides (vancomycin and teicoplanin) become the only therapeutic choice for many years. According to current guidelines, vancomycin still represents the first line antibiotic therapy for the treatment of MRSA bloodstream infections, along with daptomycin [49, 74]. Indeed, despite

newer anti-MRSA drugs, including linezolid or fifth generation cephalosporins, were introduced in recent years, clinical trial demonstrating their superiority over vancomycin are lacking. Nevertheless, some concerns related to vancomycin-based therapy are noteworthy. As first, according to 2020 IDSA Guidelines update concerning therapeutic monitoring of VAN, the latest recommendation advocates for AUC-based dosing and monitoring of VAN, utilizing PK equations or Bayesian modeling. The guidelines propose the maintenance of the AUC within the range of 400 to 600 mcg*h/mL to mitigate the risks of clinical failure and the occurrence of acute kidney injury (AKI). These concentrations are achieved at VAN doses of 15–20 mg/kg (based on actual body weight) administered every 8–12 hours as an intermittent infusion for most patients with normal renal function [75]. , For VAN MIC > 1 mg/L, doses of 15-20 mg/kg administered every 8-12h may fail to achieve the AUC, but higher doses could increase the risk of nephrotoxicity. For that, new guidelines suggest against the use of VAN if MIC is > 1 mg/L. [75]. Moreover, vancomycin has a low bactericidal activity, and its efficacy may be hindered by high inoculum MRSA infection [76]. Finally, nephrotoxicity is a common adverse event complicating therapy with vancomycin in 5%–35% of cases, according to different studies [77]. More recently, a lipopeptide antibiotic, daptomycin, was approved for the treatment of complicated skin and skin-structure infections and for treatment of *S. aureus* BSI and right-sided endocarditis, since it showed non-inferiority in mortality if compared to standard of care in randomized controlled trials [78]. In addition, in real-world studies, daptomycin has shown to have a higher bactericidal activity than vancomycin, with a better safety profile [79] and to be associated with a higher clinical cure of MRSA bacteremia, independently from vancomycin MIC [80].

Additionally, another anti-MRSA antibiotic belonging to oxazolidinone family, linezolid, was approved for the treatment of community-acquired and nosocomial pneumonias and skin and soft-tissue infections caused by MRSA [81]. Linezolid could be considered as a salvage therapy for persistent MRSA bacteremia [82, 83]. Results of a recent meta-analysis showed that linezolid is comparable to glycopeptides and daptomycin in terms of mortality, clinical and microbiological cure and safety [84]. However, its utilization as first line for MRSA BSI treatment has some issues, including the high volume of distribution (50–60 L) and the low protein binding to albumin (from 10.5 to 31%), resulting in a high tissue distribution and lower bloodstream concentration, theoretically limiting its use in the context of BSIs [85]; consequently, therapeutic drug monitoring is warranted to optimize therapy with this drug [86]. Moreover, drug-drug interactions and risk of

toxicity (neuropathy and myelosuppressive effect) should not be neglected when linezolid is prescribed. Nevertheless, linezolid can be administered through an oral formulation, giving the chances to perform an early switch in low-risk patients with MRSA BSI, leading to a reduced duration of hospitalization [87]. Another molecule included in oxazolidinone family is tedizolid, which demonstrated the noninferiority compared to linezolid in the early clinical response rate; in addition, tedizolid showed a favorable safety profile in terms of gastrointestinal and hematological side effects [88].

Teicoplanin is not recommended as fist line regimen for MRSA bacteraemia. Anyway, it could be considered as second-line regimen, when first-line regimens are contraindicated. [89] Evidence on its efficacy are limited, but no inferiority has been documented compared with vancomycin [90], especially using higher maintenance dosing. [91].

The current efficacy profile, toxicity and other limitations of VAN\Teicoplanin, DAP, and Linezolid\Tedizolid for MRSA bacteraemia are summarised in a Table 2.

*3.2 Combination therapy versus monotherapy for Staphylococcus aureus bloodstream infections*The treatment of S.aureus BSI remains challenging for clinicians, despite the availability of different treatment options. Indeed, despite many guidelines suggest monotherapy with VAN or DAP, many clinicians still prefer the use of combination therapy, with two or more drugs, according to site of infection and severity of MRSA BSI. This uncertainty regarding what is the optimal treatment causes a jeopardized management worldwide, even in clinical trial design, where adjunct antibiotic therapy is often allowed [92].

The combination therapy based on vancomycin or daptomycin plus a ß-lactam has been proposed as a strategy for facing this treat, for both MSSA and MRSA. Other strategies included a combination of two ß-lactams; for instance, Ulloa et al. suggest the combination of cefazolin with ertapenem for treatment of refractory MSSA BSI; this combination results successful *in vitro*, since the two drugs bind complementary penicillin binding protein; moreover, the *in vivo* studies show cooperativity with innate immune system [93]. Conversely, studies about combination therapy with β-Lactam and daptomycin for MSSA infections suggest that this combination does not improve the outcome or the duration of bacteremia and mortality [94,95].

Nevertheless, it is well described that β-lactam activity improves when vancomycin or daptomycin susceptibility decreases; otherwise, the re-sensitisation to a β-lactam of a daptomycin resistant MRSA strain may also occur; this phenomenon is known as "*seesaw effect"* and involve mutations at the mprF locus [96,97]. The first trial on combination therapy for MRSA BSI, conducted by CAMERA study group [98], suggested that the addition of an anti-staphylococcal β-lactam to vancomycin may shorten the duration of MRSA bacteremia. A further trial [99] was conducted hypothesizing that vancomycin or daptomycin plus an anti-staphylococcal β-lactam would improve clinical outcomes of patients with MRSA BSI; the study concluded that no significant improvement was obtained in patients treated with combination therapy in term of mortality, persistent bacteremia, relapse, or treatment failure. However, the study was interrupted earlier due to higher risk of kidney failure in the combination group, especially in patients undergoing flucloxacillin. . Conversely, the preliminary result of a study investigating the duration of bacteremia in course of therapy daptomycin plus ceftaroline versus Standard of Care Monotherapy [100] show a significant difference in in-hospital mortality, with higher mortality rate in standard of care group. The study was interrupted early due to safety concerns.

However, recent meta-analysis on β-lactams combined with vancomycin or daptomycin for MRSA BSI show that the combination therapy significantly reduced the risk of clinical failure or recurrence of bacteremia, but has not a significant impact on mortality; however, the risk of adverse events, including *C.difficile* infection, is higher with combination therapy [101 - 103]. Similar results emerged from a recent trial on combination therapy based on fosfomycin plus daptomycin versus daptomycin in monotherapy [104].

Finally, the combination of daptomycin plus ceftaroline could be considered as an important option in case of persistent bacteremia [105], due to the synergistic effect, the anti-staphylococcal activity of ceftaroline, and the reduction of resistance rate of daptomycin in association with a ß-lactam.

4. General characteristics of fifth generation cephalosporins

Ceftaroline and ceftobiprole share common pharmacokinetic (PK) features with traditional and novel beta-lactams, showing a low volume of distribution (Vd) (36 and 21.7 L for ceftaroline and ceftobiprole, respectively), low protein binding (15-28% for ceftaroline and 16% for ceftobiprole), and predominant renal clearance (>80% for both drugs) [106 - 108].

In regard to pharmacokinetic/pharmacodynamic (PK/PD) relationship, fifth generation cephalosporins exhibit time-dependent bacterial killing similarly to other beta-lactams, being their efficacy associated with the percentage of the dosing interval that the unbound concentration is maintained above the minimum inhibitory concentration (MIC) of the targeted pathogen (%$fT_{>MIC}$) [109].

The PK/PD relationship of ceftaroline and ceftobiprole was assessed in both preclinical and clinical studies. Specifically, an *in vitro* PK model investigated the antibacterial effect of ceftaroline at labelled dosing against both methicillin-susceptible (MSSA) and -resistant *Staphylococcus aureus* (MRSA) strains exhibiting a wide range of MICs [110]. The %$fT_{>MIC}$ was found as the best PD parameter describing ceftaroline efficacy, being a 24.5%$fT_{>MIC}$, 27.8%$fT_{>MIC}$, and 32.1%$fT_{>MIC}$ associated with bacteriostatic, 1-log-kill, and 2-log-kill activity, respectively [110]. Notably, changes in ceftaroline population analysis profiles were significantly related to $fT_{>MIC}$, considering that a $fT_{>MIC}$ <50% was associated with *S. aureus* regrowth showing four-fold increased MIC to ceftaroline after 96 h of drug exposure. This finding was consistent with current evidence supporting the need of more aggressive beta-lactams PK/PD targets for suppressing resistance emergence [111-113]. Similarly, in an *in vitro* hollow-fiber infection model in which MRSA isolates exhibiting high ceftaroline MICs (i.e., 2-4 mg/L), a $fT_{>MIC}$ of 29%, 32%, and 35% was associated with bacteriostatic, 1-log-kill, and 2-log-kill activity, respectively [114]. Furthermore, a ceftaroline dosing of 600 mg q8h allowed a sustained long-term bacterial suppression against MRSA isolated exhibiting high ceftaroline MICs [114]. In regard to clinical studies, the relationship between ceftaroline PK/PD target attainment and clinical/microbiological response was assessed in patients affected by acute bacterial skin and skin structure infections (ABSSSIs) enrolled in pivotal trials [115]. A $fT_{>MIC}$ threshold of 54.2% and 55.0% was significantly associated with microbiological response when all patients were included (p=0.001) or only those with *S. aureus* infections were considered (p=0.023), respectively [115]. Furthermore, at multivariate analysis the occurrence of a $fT_{>MIC}$ > 54.2% and 55.0% was an independent predictor of microbiological response [115]. Conversely, no significant relationship between ceftaroline %$fT_{>MIC}$ and microbiological and/or clinical outcome was found in patients affected by community-acquired pneumonia (CAP), mainly due to the fact that most patients had a $fT_{>MIC}$ values ranging between 91.7% and 100.0% [116].

In regard to ceftobiprole, a preclinical model found that, similarly to ceftaroline, the %$fT_{>MIC}$ was found as the best PD parameter describing ceftobiprole efficacy, being a 36-45%$fT_{>MIC}$, 14-28%$fT_{>MIC}$, and 15-22%$fT_{>MIC}$

associated with bacteriostatic activity against *Enterobacterales*, *S. aureus*, and *S. pneumoniae*, respectively [117]. Higher PK/PD targets were associated with 2-log-kill bactericidal activity, being a $fT_{>MIC}$ values of 64.5%, 29.3%, and 25.8% required for *Enterobacterales*, *S. aureus*, and *S. pneumoniae*, respectively [117]. In regard to clinical studies, the relationship between ceftobiprole PK/PD target attainment and clinical/microbiological response was assessed in patients affected by nosocomial pneumonia enrolled in pivotal trials [118]. A $fT_{>MIC}$ threshold of 51.1% and 62.2% was significantly associated with clinical cure ($p=0.0024$) and microbiological eradication ($p<0.0001$), respectively [118]. Furthermore, at multivariate analysis the occurrence of a $fT_{>MIC} > 51.1\%$ was an independent predictor of clinical cure [118].

PK/PD relationship of fifth-generation cephalosporins was poorly investigated in special populations, particularly in patients undergoing continuous renal replacement therapy (CRRT) [119–121] and/or those treated with extracorporeal membrane oxygenator (ECMO) support [122]. Notably, a recent retrospective cohort study including 35 patients with suspected ECMO-related cannula infections who received ceftobiprole as empirical treatment (of which seven after ECMO removal) found no significant differences in ceftobiprole PK behaviour between ECMO and non-ECMO patients [122]. Conversely, the occurrence of acute kidney injury requiring CRRT and/or the existence of augmented renal clearance (ARC) were associated with significant decrease in ceftobiprole serum levels [122].

Considering their time-dependent activity, both ceftaroline and ceftobiprole may benefit from prolonged and/or continuous infusion for maximizing PK/PD targets [109]. Some studies suggested that in the treatment of critically ill patients affected by ventilator-associated pneumonia (VAP) and/or exhibiting ARC, continuous infusion may allow the attainment of optimal ceftaroline PK/PD targets against MRSA compared to intermittent infusion [123,124]. Similarly, prolonging ceftobiprole infusion over 4h was found to ensure the attainment of optimal PK/PD targets against pathogens exhibiting a MIC of 4 mg/L (equal to the EUCAST non-species-specific breakpoint) also in critically ill ventilated patients showing augmented renal clearance (ARC) [125].

The attainment of optimal PK/PD targets at site of infection represents a relevant feature that should be taken into account when fifth generation cephalosporins are used for the treatment of secondary bacteremia caused by MRSA. Ceftaroline and ceftobiprole penetration rate and PK/PD target attainment in different infection sites were summarized in **Table 3**. Penetration rate of ceftaroline and ceftobiprole in different sites was similar

355 to those of other cephalosporins [126]. Adequate penetration was found in muscle (approximatively 50% and
356 70% for ceftaroline and ceftobiprole, respectively) and soft/adipose tissue (47%-58% for ceftaroline and 49%
357 for ceftobiprole) [127-129], whereas poor/limited penetration rate was reported in deep-seated infections
358 (approximatively 25% in epithelial lining fluid [123,130,131], and <10% in bone [132].
359 Cerebrospinal fluid penetration of CPT and BPR are still under investigation. In an animal model, Helfer et al.
360 observed that the brain penetration of CPT was impacted by MRSA infection, rising from 17% in healthy
361 animals to 27% in infected animals. Simulations of a 2-hour intravenous infusion at a dosage of 50 mg/kg
362 every 8 hours resulted in >90% PTA in both plasma and brain for MRSA MIC value of 0.25 mg/L, suggesting
363 that the drug should be considered an option for treating CNS infections.. [133] In a study involving 12 healthy
364 volunteers and 9 neurosurgical patients, Helfer and colleagues conducted simulations considering varying
365 levels of meningeal inflammation. For a CPT MIC of ≤1 mg/L, CSF penetration of CPT was 4%. However,
366 this penetration would increase to 19% in the presence of mild meningeal inflammation (reaching PTAs of
367 34% and 9.1% for dosages of 600 mg q8h and q12h, respectively) and further rise to 62% in the case of fully
368 inflamed meninges, reaching PTAs of 99.8% and 97.2% for 600 mg q8h and q12h, respectively. [133]. Clinical
369 data in real life are limited to case reports, documenting the clinical efficacy of CPT for the treatment of CNS
370 infections caused by MRSA, despite the limited penetration of ceftaroline documented into the CSF in those
371 works [134 - 136]. Limited data exists regarding the CSF penetration of BPR. Stucki et al. observed that the
372 penetration of BPR was approximately 16% in inflamed meninges, and 2% in uninflamed meninges in a rabbit
373 meningitis model [137], but clinical data are not available. Optimal PK/PD target attainment at site of infection
374 (i.e., 100%$fT_{>4\text{-}8xMIC}$) was found only with the use of high-dose ceftaroline administered by continuous infusion
375 (i.e., 600 mg q8h over 8h infusion) [123].
376
377 *4.1 Ceftaroline: approved indications and data from randomized controlled trials*
378 Ceftaroline is currently approved for the management of community-acquired pneumonia (CAP) and
379 complicated skin and soft tissue infections (cSSTIs) at the dosage of 600 mg q12h over 1-h infusion 140-144].
380 Features of pivotal trials are summarized in **Table 4**.
381 In regard to CAP, two phase III RCTs (FOCUS 1 and 2) were conducted with ceftaroline in this clinical scenario
382 [140, 142]. In FOCUS 1 trial, 606 patients affected by CAP were randomized to ceftaroline 600 mg q12h

(n=298) or ceftriaxone 1 g/day (n=308) [140]. Bacteremia was reported in less than 3% of overall cases, whereas MRSA was isolated in 10 out of 298 patients (3.4%) randomized to ceftaroline. A significant higher clinical cure rate was reported in patients receiving ceftaroline compared to ceftriaxone (86.6% vs. 78.2%; difference 8.4%; 95%CI 1.4%-15.4%), whereas no significant difference between the two groups emerged in terms of microbiological eradication rate in MRSA subgroup (80.0% vs. 64.3%; difference 15.7%; 95%CI -23.0%-48.0%). Similarly, no difference in terms of treatment-emergent adverse events (AEs) were found between groups (39.9% vs. 44.2%) [140]. In FOCUS 2 trial, 622 patients affected by CAP were randomized to ceftaroline 600 mg q12h (n=315) or ceftriaxone 1 g/day (n=307) [141]. Bacteremia was reported in approximatively 5% of enrolled patients, whereas MRSA was detected in 15 out of 315 patients (4.8%) randomized to ceftaroline. No significant difference emerged between groups in terms of clinical cure rate (82.1% vs. 77.2%; difference 4.9%; 95%CI -2.5%-12.5%). Similarly, in MRSA subgroup no significant differences were found in microbiological eradication (66.7% vs. 56.3%; difference 10.4%; 95%CI -23.8%-42.2%). The proportion of treatment-emergent AEs was similar between groups (20.3% vs. 16.9%) [32]. In FOCUS and FOCUS 2 trials, ceftaroline resulted non-inferior in clinical response at day 4, end of therapy, and test of cure compared to ceftriaxone for the treatment of bacteremia associated to community acquired pneumonia (CAP), mainly caused by *S. pneumoniae* followed by *S. aureus* [142].

Furthermore, a specific phase III RCT comparing ceftaroline and ceftriaxone in CAP scenario was conducted among 847 Asian patients reporting consistent findings with FOCUS 1 and 2 trials, although the proportion of bacteraemic patients and/or those with MRSA isolation was only 1% [143].

In regard to cSSTIs, two phase III RCTs (CANVAS 1 and 2) were conducted with ceftaroline in this clinical scenario [144, 145]. In CANVAS 1 trial, 702 patients affected by cSSTIs were randomized to ceftaroline 600 mg q12h (n=353) or vancomycin 1 g q12h plus aztreonam 1 g q12h (n=349) [144]. Bacteremia was reported in 4.4% of enrolled patients, whereas MRSA was isolated in 93 out of 353 cases (26.3%) randomized to ceftaroline. No significant difference emerged between groups in terms of clinical cure rate (91.1% vs. 93.3%; difference 2.2%; 95%CI -6.6%-2.1%). Similarly, no significant difference was found in terms of clinical cure between ceftaroline and comparators in MRSA subgroup (95.1% vs. 95.2%). Proportion of treatment-related AEs was similar among groups (47.0% vs. 48.1%) [144]. In CANVAS 2 trial, 694 patients affected by cSSTIs were randomized to ceftaroline (n=348) or vancomycin plus aztreonam (n=346) at the same dosing schedule

411 implemented in CANVAS 1 trial [145]. Bacteremia was found in 3.5% of included cases, whereas MRSA was
412 isolated in 86 out of 348 patients (24.7%) randomized to ceftaroline. No significant difference emerged
413 between groups in terms of clinical cure rate (92.2% vs. 92.1%; difference 0.1%; 95%CI -4.4%-4.5%).
414 Similarly, no significant difference was found in terms of clinical cure between ceftaroline and comparators in
415 MRSA subgroup (91.4% vs. 93.3%). Proportion of treatment-related AEs was similar among groups (42.2%
416 vs. 46.9%) [145].
417 Notably, a small RCT including 40 patients affected by MRSA bloodstream infections, of which 17 were
418 randomized to combination therapy with daptomycin plus ceftaroline and 23 received daptomycin or
419 vancomycin monotherapy, was prematurely interrupted because of significant higher in-hospital mortality rate
420 in monotherapy arm (6/23 vs. 0/17; p=0.029) [141]. A subgroup analysis suggested that the survival benefit
421 may be limited to patients with high-risk endovascular sources and those with IL-10 levels > 5 pg/ml on the
422 day of first positive blood culture [146].
423
424 *4.2 Ceftobiprole: approved indications and data from randomized controlled trials*
425 Ceftobiprole is currently approved for the management of CAP and hospital-acquired pneumonia (HAP) at the
426 dosage of 500 mg q8h over 2-h infusion [1147,148]. Features of pivotal trials are summarized in **Table 4**.
427 Nicholson *et al*. [147] randomized 638 patients affected by CAP to ceftobiprole (n=314) or ceftriaxone plus
428 linezolid (n=324). Bacteremia was detected in 4% of enrolled patients, whereas MRSA was isolated in only
429 one of the patients randomized to ceftobiprole. No significant differences between the two groups were found
430 in terms of clinical cure (86.6% vs. 87.4%) or microbiological eradication (88.2% vs. 90.8%). Conversely, a
431 significant higher proportion of treatment-related AEs were reported in patients receiving ceftobiprole (36%
432 vs. 26%; 95%CI 2.9%-17.2%) [147].
433 Awad *et al*. [148] randomized 781 patients affected by HAP or VAP (26.9% of overall enrolled cases) to
434 ceftobiprole (n=391) or combination therapy including ceftazidime plus linezolid (n=390). 10.5% of patients
435 were bacteraemic, whereas MRSA was isolated in 41 out of 391 cases (10.5%) receiving ceftobiprole. No
436 significant differences between the two groups were reported in terms of overall cure rates both in intention-
437 to-treat (49.9% vs. 52.8%) and clinically evaluable analysis (69.3% vs. 71.3%). Similarly, no significant
438 differences between groups were found in clinical cure (63.0% vs. 64.0%) and microbiological eradication rate

(48.0% vs. 57.0%) in MRSA subgroup. Notably, in VAP subgroup, a significant lower clinical cure (23.1% vs. 36.8%; 95%CI −26.0% - −1.5%) and microbiological eradication rate (30.4% vs. 50.0%; 95%CI −38.8% - −0.4%) was found in patients treated with ceftobiprole. It is noteworthy that in MRSA subgroup, after excluding VAP, ceftobiprole was associated with a significant clinical improvement at day-4 compared to ceftazidime plus linezolid (94.7% vs. 52.6%; 95%CI 17.5%-66.7%). No difference in treatment-related AEs was reported between the two groups (24.9%-25.4%) [148].

Recently, the phase III TARGET trial randomized 679 patients affected by acute bacterial skin and skin structure infections (ABSSSIs) to ceftobiprole (n=335) or vancomycin plus aztreonam (n=344) [149]. MRSA was isolated in 82 out of 335 patients (24.5%) receiving ceftobiprole. No significant difference in early clinical response was found between two groups at intention-to-treat analysis (91.3% vs. 88.1%), whereas a significant higher early clinical response was reported in ceftobiprole group at clinically evaluable analysis (94.3% vs. 89.4%; 95%CI 0.6%-9.4%). In MRSA subgroup, no significant difference was found between groups in terms of microbiological eradication (93.9% vs. 91.8%). In regard to safety, no significant difference emerged between patients receiving ceftobiprole or vancomycin plus aztreonam (44.3% vs. 38.6%) [149].

5. Safety and effectiveness of fifth generation cephalosporins in "real-world" studies

Even if ceftaroline and ceftobiprole were originally approved only for treatment of pneumonia or acute bacterial skin and skin structure infections (ABSSSI) [106, 125], once entered the clinical practice their sprawling potential immediately emerged so much that currently their use for off-label indications is almost prevailing especially for bacteremic infections.

Indeed, between 2015-2016 ceftaroline received the FDA approval for the treatment of *S. aureus* bacteremia associated with ABSSSI in adults and children [106].

Real-world studies on ceftaroline and ceftobiprole have been growing, possibly expanding their place in therapy not only as rescue in refractory *S. aureus* infections but also as first-line treatment of primary or complicated disease, in monotherapy or in combination with other drugs.

As for safety, ceftaroline and ceftobiprole showed a high tolerability similarly to other cephalosporins.

5.1 Safety and effectiveness of ceftaroline in "real-world" studies: focus on bloodstream infections

Thought no targeted RCTs are available, data on effectiveness of use of ceftaroline on BSIs are encouraging, especially for complicated infections. Characteristics and outcomes of studies investigating combination regimens with ceftaroline for *S. aureus* bacteremia are shown in **Table 5**.

A recent metanalysis assessed outcomes between patients receiving combination of ceftaroline plus vancomycin or daptomycin versus vancomycin or daptomycin monotherapy for MRSA BSIs. Six of the studies reported in **Table 5**were included, 1 randomized trial and 5 retrospective studies. Rate of in-hospital mortality, duration of bacteremia, and adverse events were similar among the two groups. Bacteremia recurrence was significantly lower with combination treatment (OR = 2.95, 95% CI= 1.22–7.15, p = 0.02, I2 = 6%) [150].

Data from CAPTURE, namely the US Clinical Assessment Program and Teflaro® Utilization Registry, were related to *S. aureus* bacteremia secondary to CAP, ABSSSI and endocarditis and showed clinical success rate ranging from 58-71% among all patients and 50-77% in MRSA infections [151]. First real-world reports focusing on ceftaroline for *S. aureus* BSIs concerned generally savage therapy after failure of first-line regimens. Frequently, off-label dosage of 600 mg every 8h was administered.

Moreover, many case series described use of ceftaroline alone or in combination as rescue-therapy after emergence of vancomycin or daptomycin resistant strains, persistent BSIs or bacteremic deep-seated infections, demonstrating a notable rate of clinical success overall, both against MSSA [152] and MRSA [152-155].

Epidemiological studies enrolling patients treated with ceftaroline for different indications, provided more consistent data on effectiveness of ceftaroline in *S. aureus* BSIs.

A retrospective study analyzed a large cohort of 527 hospitalized patients receiving ceftaroline for at least 72 hours. One hundred forty-eight patients were treated for *S. aureus* bacteremia, mainly MRSA (92.5%). A combination regimen was used in 30.8% patients, generally with metronidazole. Clinical and microbiological success occurred in 78.3% and 90.8% patients, respectively. However, over-all mortality (7.6%) was mainly attributable to bacteremia which had the highest mortality rate (14.2%) compared to other infections. Moreover, patients with bacteremic *S. aureus* endocarditis and pneumonia had the highest rate of clinical failure and mortality (22.9% and 20%) [156].

494 A multicenter observational study described 211 patients treated with ceftaroline for MRSA BSIs mostly
495 associated with pneumonia and endocarditis. A combination with an anti-MRSA drug (primarily daptomycin)
496 was chosen for 21.8% patients. Clinical cure occurred in 68.3% (69.7% in the monotherapy and 64.9% in the
497 combination group, respectively) and the median BSI durations post-ceftaroline treatment were 2 days (IQR
498 1-4 days) for monotherapy and 3 days (IQR 1.5-5 days) for combination. Independent predictors of failure at
499 multivariable logistic regression analysis were higher acute physiology and chronic health evaluation II
500 (APACHE II) and malignancy [157].
501 In another retrospective population-based study, among 764 patients afferent to the US Veterans Health Care
502 System and treated with ceftaroline for different indications, 87 had bacteremia. In this subset, median in-
503 hospital length of stay of 8 days (IQR, 3-18), in-hospital mortality was 6% while 30-day hospital readmission
504 rate was the highest among all infection types (48% vs 33% overall), however reasons of readmission were
505 unknown [158].
506 Being MRSA bacteremia still considered a serious illness associated with high rate of morbidity and mortality,
507 many comparison studies investigated effectiveness of ceftaroline with respect to other anti-MRSA first-line
508 agents.
509
510 Mootz et al performed a retrospective study on 409 patients treated with ceftaroline (N=67) or daptomycin
511 (N=342) as first-line agent for MRSA sepsis. A partner drug was frequently used in both groups, particularly
512 piperacillin/tazobactam (ceftaroline=1% vs daptomycin=26%), ciprofloxacin (ceftaroline=1% vs
513 daptomycin=9%), and vancomycin (ceftaroline=24% vs daptomycin =11%). Unadjusted hospital readmission
514 rates for ceftaroline and daptomycin, respectively, were: 30-day (25%/37%, p = 0.06), 60-day (27%/44%, p =
515 0.008), and 90-day (28%/46%, p = 0.01). Unadjusted mortality rates were: in-hospital (7%/12%, p = 0.4), 30-
516 day (3%/9%, p = 0.1), 60-day (6%/12%, p = 0.2), and 90-day (7%/15%, p = 0.1). At multivariable analysis,
517 use of ceftaroline was less associated with both 30/60/90-day hospital readmission (OR 0.54, 95% CI 0.29–
518 0.98; OR 0.42, 95% CI 0.23–0.76; OR 0.42, 95% CI 0.23–0.75) and 30/60/90-day mortality (OR 0.23, 95%
519 CI 0.04-0.82; OR 0.34, 95% CI 0.10–0.93; OR 0.34, 95% CI 0.11–0.86) [159].
520 Zasowski et al investigated outcomes of 270 patients with MRSA bacteremia treated with ceftaroline (N=83)
521 or daptomycin (N=187) as single agent. Patients had mainly received vancomycin before starting a study drug

but all for <96h from BSI onset. Ceftaroline showed non-inferiority to daptomycin regarding to composite treatment failure defined as 30-day mortality, bacteremia duration ≥7 days, and 60-day BSI recurrence (39% daptomycin, 32.5% ceftaroline; weighted risk difference, 7.0% [95% CI, –5 - 19%]). No differences were also found for secondary outcomes including each single component of primary outcome, 60-day readmission related to MRSA bacteremia, BSI duration post–study drug introduction, and length of stay post–study drug initiation. [157].

In a cohort study where 30 patients treated with ceftaroline for MRSA bacteremia with a vancomycin MIC >1.0 mg/l were compared with a matched control group of 102 patients with MRSA BSIs treated with daptomycin (N=46) or vancomycin (N=56). Bacteremia was mainly associated with endocarditis, ABSSSI and bone/joint infections. The 30-day mortality rate was 13% (n=4) in the ceftaroline group, 24% (n=11) in the daptomycin group and 11% (n=6) in the vancomycin group (p=0.188) [160].

Finally, in another multicenter, case–control study, 32 patients with MRSA infection (vancomycin MICs ≥ 2 mcg/mL) were matched 1:1 to receive ceftaroline -empirically or after vancomycin failure- or to receive vancomycin or an alternative antibiotic active against MRSA (excluding ceftaroline). In the ceftaroline group, median duration of previous vancomycin therapy was 5 days (IQR 3–15.8 days). Time to eradication of MRSA BSI was significantly shorter after ceftaroline compared with vancomycin [4 days (IQR, 3–7.5 days) vs 8 days (IQR, 5.8–19.5 days); P = 0.02]. In the ceftaroline group rate of clinical success was higher as well as rate of recurrence at day 7 was lower than in the control group, though difference not statistically significant for both outcomes (81% vs. 44%, p=0.06 and 6% vs 38%, p=0.08, respectively) [161].

Treatment with ceftaroline is generally well tolerated, even if some safety concerns emerged in post-marketing period especially associated with off-label higher dosage and duration.

Rate of AEs collected from large cohort studies ranged from <1% to 9% and consisted mainly with rash, nausea/vomiting, acute kidney injury (AKI), neutropenia, eosinophilia, leukocytosis, anemia, thrombocytopenia, and *C. difficile* infection. Myalgia/myositis and elevation of creatine phosphokinase were also described especially in combination with daptomycin [157-162].

Neutropenia is the most common hematologic AE associated with ceftaroline. A recent review including 37 episodes of ceftaroline-associated neutropenia. The event occurred after a median of 25 (range 8–125) days from antibiotic introduction, with a median duration of neutropenia (range) of 4 (1–16) days. Around half of

patients experienced severe neutropenia (absolute neutrophil count [ANC] nadir <100/mmc). The overall incidence of neutropenia when ceftaroline was administered for ≥7–14 days was 12% [163].

5.2 Safety and effectiveness of ceftobiprole in "real- world*" studies: focus on bloodstream infections*

Recently, the results of the ERIDICATE trial on use of ceftobiprole for *S. aureus* bacteremia have been published. [164]. Overall, 390 patients were enrolled, of these 387 were in the modified intent-to-treat population and received ceftobiprole (N=189) or daptomycin with or without optional aztreonam (N=198). Rate of MRSA BSI was 24.3%. Ceftobiprole was non inferiority to daptomycin at the primary endpoint of 70-day clinical success rate (69.8% vs 68.7% respectively, adjusted difference 2.0%, 95% CI -7.1% to 11.1%) [164].

Previously, limited data derived from prior RCTs on pneumonia and ABSSII as well as real-world experiences have already heralded the beneficial outcomes of BSIs treated with ceftobiprole.

Rello et al presented at 2016 European Society of Clinical Microbiology and Infectious Diseases Congress (ECCMID) an interesting post-hoc analysis of four phase 3 RCTs, including 2 on ABSSSI [165, 166] 1 on CAP [167] and 1 on HAP/VAP [168] assessing outcomes of 95 patients with secondary staphylococcal BSIs treated with ceftobiprole (N=45) or the other comparator treatment that were vancomycin [166], vancomycin plus ceftazidime [165], ceftriaxone plus optional linezolid [167] and ceftazidime plus linezolid [168] (N=50). Patients receiving ceftobiprole or the comparator regimen have similar clinical success rate (48.9% and 44% respectively, difference 4.9%, 95% CI −12.2 to 25.0) and 30-day crude mortality (8.9% and 16%, respectively, difference −7.1%, 95% CI −20.2 to 6.0). Moreover, in a subset of 18 patients with MRSA BSI a trend toward better outcome was observed among patients receiving ceftobiprole (clinical cure, 55.6% [5/9] vs. 22.2% [2/9], respectively, difference 33.3%, 95% CI −9.0 to 77.7; 30-day all-cause mortality, 0.0% [0/9] vs. 22.2% [2/9], respectively, difference −22.2%, 95% CI −49.4 to 4.9) [169].

To date, reports on real-world use of ceftobiprole are limited. The well-known clinical effectiveness of combination of daptomycin and other anti-staphylococcal beta-lactams [105, 170] along with the proven in-vitro synergy of daptomycin and ceftobiprole [171] has frequently prompted clinicians to choose this regimen for difficult-to treat *S. aureus* infections.

577 The CEFTO-CURE study explored real-world use of ceftobiprole in 10 Italian centers. Among 195 patients,
578 prevalent indications for using ceftobiprole were pneumonia (151/195, 74%), and BSIs (37/195, 19%).
579 Ceftobiprole was usually administered empirically (127/195, 65%), in combination regimen (129/195, 66%)
580 mostly with meropenem (40/129, 31%), and in case of pneumonia (91/129, 71%) and BSI (26/129, 20%). The
581 others received ceftobiprole alone (66/195, 34%), generally when pneumonia was diagnosis (60/66, 91%). A
582 microbiological diagnosis was achieved in 39% (76/195) of cases; MRSA was more frequently involved (38%,
583 29/76). Excluded 12 patients with diagnosis of microorganisms non susceptible to ceftobiprole, the failure rate
584 was 21% (39/183) and the crude all-cause mortality rate was 19.6% (36/183) and the attributable mortality rate
585 was 6% (11/183). Among 35 patients with bacteremia, 74% had clinical success while 23% died. At the
586 multivariable analysis performed with the multi-level model, main variables related with clinical success were
587 male gender, identification of causative microorganism, diagnosis of pneumonia while diagnosis of sepsis
588 predicted failure. At the multivariable analysis performed with the multi-level model, main variables associated
589 with all-cause mortality was age, higher comorbidities, hospital-acquired infection, mechanical ventilation,
590 sepsis, and clinical failure; survival was associated with COPD, identification of causative pathogen and
591 duration of ceftobiprole therapy. Performing inverse probability of treatment weighting (IPTW) analysis
592 adjusted for baseline characteristics of patients who received ceftobiprole as monotherapy and patients treated
593 with combination regimen, no significant differences were found between these two groups with respect to
594 clinical success (IPTW OR of monotherapy vs combination therapy 1.19, 95% CI 0.40–3.45) or all-cause
595 mortality (IPTW OR of monotherapy vs combination therapy 0.76, 95% CI 0.22–2.69) [172].
596 Another Italian retrospective study compared data on real-world use of ceftaroline (N=75) and ceftobiprole
597 (N=63). Rate of bacteremia/endocarditis was 17% (24/138). Main pathogen isolated from culture was MRSA
598 (29.3%). Combination therapy was the most common strategy among groups, more frequently with
599 daptomycin. Patients treated with ceftobiprole had significantly higher comorbidities; moreover, in this group
600 significant higher rate of multisite, nosocomial, and culture-negative infections was also found. In-hospital
601 mortality, length of stay, and rates of clinical cure, improvement or failure were similar between groups. In
602 multivariable model, *S. aureus* infection was the only significant predictor of outcome [173].
603 Data of 38 patients treated with ceftobiprole were provided from the CLEAR (Canadian LEadership on
604 Antimicrobial Real-life Usage) registry. Overall, 92.1% patients had bacteremia: 2.6% were primary BSIs, the

other were associated to endocarditis, osteomyelitis, and HAP. Infections were commonly caused by MRSA (94.7%). Ceftobiprole was generally chosen as second-line therapy ought to failure of (71.1%), resistance to (18.4%) or adverse effects from (10.5%) antibiotics previously administered. Combination regimen with daptomycin (55.3%) or vancomycin (18.4%) was frequently preferred. Clinical and microbiological cure occurred in 84.8% and 97% of patients, respectively [174].

Some case report/series shared the successful clinical and microbiological outcomes of patients treated for severe bacteremic infections with ceftobiprole mostly associated with daptomycin or vancomycin: 1 patient with MRSA prosthetic valve endocarditis [175], 6 with MRSA BSI derived from vary deep-seated infections [176] and 12 with endocarditis mainly caused by oxacillin-susceptible and resistant *S. aureus* and coagulase-negative *Staphylococci* (CoNS) [177].

Another case series described 21 patients with ampicillin-susceptible *E. faecalis* BSI (61% secondary to left-sided endocarditis) treated with combination of ceftobiprole and ampicillin. Mean duration of this regimen was 20.4 ± 11.1 days, and a subsequent oral treatment was chosen for 6 patients. The majority of patients experienced clinical cure (81%) and blood culture clearance (86%). Only one patient relapse after withholding of the partial oral treatment [178].

Safety profile of ceftobiprole observed in phase 3 trials showed a high number of AEs (ranging from 36% to 63%) causing 4-6% rate of treatment discontinuation; similar percentage was found for the comparative drugs. Fortunately, most events were classified as mild and consisted with nausea/vomiting, infusion site reaction, diarrhea and headache [165-168]. Observational retrospective studies documented fewer AEs, mainly mild gastrointestinal syndrome or *C. difficile* infection, hematologic alterations like leukopenia, anemia, thrombocytopenia, or mild elevation of liver enzyme. [172,173]. One case report reported ceftobiprole-associated agranulocytosis following prolonged treatment [179].

6. Future potential place in therapy of fifth generation cephalosporins

Despite numerous real-world studies and post-hoc analyses conducted in pivotal trials on the use of fifth generation cephalosporins, the quality of evidence produced is compromised by the small patient sample sizes and the absence of specific randomized controlled trials. Concerning real-world observational studies, additional statistical analyses would be necessary in future works to enhance their power and "mimic"

randomized trials, such as propensity score matching or inverse probability of treatment adjustment weighting, which unfortunately are lacking in many works. For this reason, although fifth generation cephalosporins appear promising in the context of MRSA bloodstream infections, their use should still be approached cautiously. Nevertheless, , the interest in their place in therapy is significantly growing, especially in case of bacteremic MRSA pneumonia, when daptomycin could result a suboptimal therapy, since it is inhibited by surfactant [180]; of note, several potential use of ceftaroline and ceftobiprole for the treatment of MRSA-BSI emerged from published data, opening many research questions.

Importantly, studies showed that fifth generation cephalosporins could be a valuable monotherapy for bacteremic patients with similar clinical cure and mortality rate if compared to vancomycin or daptomycin [157-162, 164-169], considered the backbone of MRSA-BSI treatment from decades. This open the question if this paradigm may be challenged.

In fact, by looking at treatment rules of MSSA-BSI, data suggest that antistaphylococcal penicillins (ASP) or cefazolin should be preferred over glyco- or lipopeptides [71-73] for definitive antibiotic therapy. Accordingly, it is rational to investigate if ceftaroline or ceftobiprole may be an effective (or even preferable) first-line treatment for MRSA-BSIs.

In fact, the hypothesis of placing anti-MRSA cephalosporins as backbone of therapy have been introduced in several hospitals in recent years. Consequently, following initial experiences on MRSA-BSIs as salvage therapies after an initial treatment failure [152-154, 175,176, 176], subsequent works proposed a direct comparison of an anti-MRSA cephalosporins versus vancomycin or daptomycin with encouraging results: fifth generation cephalosporins were associated with a similar outcomes of daptomycin and vancomycin in large retrospective studies [157-162, 164-169], and ceftobiprole resulted non-inferior to daptomycin for the treatment of complicated MRSA-BSI [164].

Moreover, fifth generation cephalosporin are broad spectrum antibiotics, and the risk of *C.difficile* colitis should be considered; indeed, in an *in vitro* human gut model, ceftaroline can induce simulated *C.difficile* infection, as well as ceftriaxone [181]. However, the occurrence of this complication is rare in real-world studies [182], despite it is not negligible.

659 Finally, some studies suggested that ß-lactams exerted a significant activity in modulating interleukins
660 response to bacteriemia, producing a more favorable host response to infection if compared with glyco- or
661 lipopeptide, probably influencing the mortality risk [183].
662 On these bases, times to explore potential place in therapy of these drugs as first line therapy are probably
663 mature.
664 Another important area of investigation is represented by the role of fifth generation cephalosporins in
665 combination therapy for MRSA-BSI. Of note, the use of the combination of daptomycin with an anti-
666 staphylococcal beta-lactam for persistent or unresponsive MRSA infections was first published in 2004 [105,
667 184], and more recent studies confirmed the apparent superiority of this type of regimen against MRSA-BSI
668 if compared with daptomycin monotherapy [185]. However, given the intrinsic activity of
669 ceftaroline/ceftobiprole against MRSA, the association between these drugs and daptomycin may be even
670 superior to other regimens. In this sense, the recent RCT conducted by Geriak and collegues, as mentioned
671 above, was early stopped due to evident superiority of combination regimen [100], and several other reports
672 suggested that a fifth generation cephalosporins plus daptomycin may have a role in "difficult-to-treat"
673 infections [153, 172, 186, 187]. In addition, also the possible association of an anti-MRSA cephalosporins with
674 fosfomycin may be useful in selected cases, given their *in vitro* synergism [188], PK/PD characteristics of
675 fosfomycin [189] and its *in vivo* efficacy in clinical trials [104].
676 However, a final important aspect should be discussed. Available studies comparing different regimens usually
677 evaluate patients with many different sources of MRSA-BSI, including infective endocarditis, osteomyelitis,
678 low respiratory tract infections, device-related infections, central line associated BSI. Importantly, the outcome
679 of this infections is frequently influenced by other treatments, including the necessity of surgical source
680 control, or by an important diagnostic delay; so, no conclusions can be reached today about the effectiveness
681 of ceftaroline/ceftobiprole based regimens compared with other agents.
682 Similarly, other characteristics of MRSA-BSI should be analyzed, including duration of bacteriemia [190] and
683 host immunological state [191] since all these factors contribute to treatment failure and mortality. Indeed, an
684 important area of research is defining patients at high- and low-risk of mortality, in order to define place in
685 therapy of different drugs, risk of adverse events to treatments, and costs [69, 192].

686 Summarizing all these data, a possible approach to MRSA-BSI considering fifth generation cephalosporins as
687 a backbone of therapy is shown in **Figure 1**.
688
689 **7. Expert opinion**
690 Fifth generation cephalosporins represent the first ß-lactams which retain activity against MRSA. They were
691 introduced in clinical practice after being tested in non-inferiority RCTs for low-respiratory tract and skin and
692 soft tissue infections, showing to be as effective as older regimens for the treatment of these infections. In
693 addition, they showed to have a remarkable safety profile, that is in line with other cephalosporins and ß-
694 lactams and probably superior to other antimicrobial drug classes, including glycopeptides, oxazolidinones,
695 and fluoroquinolones. Sub-analysis conducted on patients with MRSA infections enrolled in RCTs confirmed
696 that ceftaroline and ceftobiprole are non-inferior to vancomycin or linezolid for the treatment of CAP, HAP
697 and ABSSSI, and could be also effective alternative in case of bacteriemic infections.
698 The interest in these preliminary data rapidly led to several exploratory "real-world" studies: fifth generation
699 cephalosporins were initially used as salvage therapy for serious MRSA endocarditis, persistent bacteriemia,
700 or in case of intolerance to other drugs with encouraging results. Subsequently, the interest moved to the use
701 of ceftaroline or ceftobiprole as first line therapies for MRSA-BSIs; of note, fifth generation cephalosporins
702 achieved similar outcomes in comparative studies versus vancomycin or daptomycin in terms of clinical cure,
703 duration of bacteriemia, risk of mortality, risk of recurrence, while a reduced risk of adverse events was noticed
704 in some cases. Finally, some clues suggested that ceftaroline and ceftobiprole may be particularly effective in
705 combination therapy with other drugs, especially daptomycin or fosfomycin, for the treatment of MRSA-BSI
706 in high-risk patients, as defined by current published scores.
707 Summarizing current knowledge, the use of anti-MRSA cephalosporins is an acceptable choice either in
708 monotherapy or combination therapy for the treatment of MRSA-BSIs, especially when associated with
709 CAP/HAP, ABSSSI, endocarditis, or persistent bacteriemia due to their relevant effectiveness and safety;
710 however, data are still inconclusive regarding place in therapy of these drugs and clinical conditions in which
711 they are preferrable over glyco- or lipopeptide or oxazolidinones. Probably, their use may be advisable in
712 combination therapy in case of severe infections or in monotherapy in subjects at higher risk of drugs-induced
713 toxicity with older regimens, given the very low incidence of adverse events with anti-MRSA cephalosporins

714 in RCTs and post-market studies; nevertheless, fifth generation cephalosporins could represent a valid
715 alternative to standard of care in case of suspected or ascertained polymicrobial infections by MRSA and gram
716 negative bacteria, in order to reduce the burden of administered antibiotic and decrease selective pressure on
717 gram negative bacteria and microbiota. On the contrary, caution should be used in case of suspected/ascertained
718 central nervous system infections due to inconsistent data regarding penetration of these drugs in cerebrospinal
719 fluid and brain tissues.
720 Despite data support the use of ceftaroline and ceftobiprole for MRSA-BSIs, many research questions are still
721 open. At first future studies should explore the correct place in therapy of these drugs in the field of severe
722 MRSA infections, including possible use in monotherapy or combination. Indeed, as explained, clinical
723 pictures associated with MRSA may be very complex, or affect patients with different comorbidities, including
724 immunocompromission or organ(s) failure; all these variables influence the outcomes and should be considered
725 by clinician at the time of antibiotic therapy prescription.
726 Future works should also define appropriate dosing strategies of these cephalosporins, including the need of
727 loading doses, extended/continuous infusions, or any further dosage adjustment according to site of infection.
728 Moreover, future studies should deeper investigate incidence and predictors of adverse events to therapy,
729 especially in those conditions at higher risk of complications, including older age, chronic kidney or liver
730 failure, or need of prolonged antibiotic therapy.
731 Finally, despite data on *in vivo* emergence of resistance to anti-MRSA cephalosporins are scarce, occurrence
732 of microbiological failure was reported and is biologically plausible; accordingly, deeper investigation is
733 needed on this topic.
734 In coclusion, fifth generation cephalosporins are valuable weapons for the treatment of MRSA-BSI, with
735 remarkable effectiveness and safety; in consideration of the epidemiological and clinical relevance of this
736 infections, further studies are warranted to implement at their best these drugs in clinical practice.
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ARTICLE HIGHLIGHTS BOX

1. Methicillin-resistant Staphylococcus aureus (MRSA) is the leading cause of bloodstream infections, causing a significant burden of morbidity and mortality.
2. The fifth generation cephalosporins (ceftaroline and ceftobiprole) represent the only ß-lactams active against MRSA.
3. Ceftaroline and ceftobiprole showed a relevant effectiveness and safety in both randomized controlled trials and observational studies involving patients with MRSA bloodstream infections.
4. Ceftaroline and ceftobiprole can be considered non-inferior to vancomycin or daptomycin for the treatment of MRSA bloodstream infections.
5. Given their pharmacokinetics/pharmacodynamics characteristics, ceftaroline and ceftobiprole may represent the backbone of MRSA bloodstream infections in mono- or combination therapy.
6. Despite many research questions are still open, including the best place in therapy of these drugs, the use ceftaroline and ceftobiprole should be considered a valuable treatment option for MRSA bloodstream infections.

DECLARATIONS

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Declaration of interest

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Author contributions

MB and DFB were involved in the conception and design of the work; DFB, AB, LB, VC, LD, and MG produced the first draft of the manuscript; MB, AS, PV, and FP revised the paper critically for intellectual content. All Authors gave the final approval of the version to be published and agree to be accountable for all aspects of the work.

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