Multi-Drug-Resistant Bacterial Infections

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Antimicrobial resistance (AMR) remains one of the top public health issues of global concern. Among the most important strategies for AMR control there is the correct and appropriate use of antibiotics, including those available for the treatment of AMR pathogens.

Keywords: antimicrobial resistance ; brand-new antibiotics ; place in therapy ; drug therapy ; emerging infectious diseases ; resistance mechanisms

1. Introduction

Antimicrobial resistance (AMR) remains one of the top public health issues of global concern and will remain so also in the wake of COVID-19 pandemic [1]. Among the most important strategies for AMR control there is the correct and appropriate use of antibiotics, including those available for the treatment of AMR pathogens. In this article, after briefly reviewing the most important and clinically relevant multi-drug-resistant (MDR) bacteria and their main resistance mechanisms, we describe the emerging antimicrobial options for both MDR Gram-positive cocci and Gram-negative bacilli, including recently marketed agents, molecules just approved or under evaluation and rediscovered older antibiotics that have regained importance due to their antimicrobial spectrum.

2. Emerging Antimicrobial Options for MDR Gram-Positive Cocci

Ceftobiprole medocaril is a fifth-generation cephalosporin approved for the treatment of hospital-acquired bacterial pneumonia (HABP), excluding ventilator-associated bacterial pneumonia (VABP), and community-acquired pneumonia (CAP). Ceftobiprole exerts its antibacterial activity by binding to important penicillin-binding proteins and inhibiting their transpeptidase activity, which is essential for the synthesis of bacterial cell walls. These include PBP2a, making ceftobiprole the only β-lactam (together with ceftaroline) active against MRSA. It is rapidly converted to the active metabolite ceftobiprole following intravenous administration [2].

Ceftobiprole has a broad spectrum of activity, notably including methicillin-resistant S. aureus and coagulase-negative Staphylococci, penicillin-resistant S. pneumoniae, and, although to a lesser extent, E. faecalis. Similar to cefepime, ceftobiprole is also active against some MDR Gram-negative bacilli, including AmpC-producing E. Coli and P. aeruginosa, but not ESBL-producing strains [3][4].

Ceftobiprole is primarily excreted renally by glomerular filtration, with minimal propensity for interaction with coadministered drugs. The recommended dose is 500 mg, administered by 2 h intravenous infusion every 8 h, with dose adjustments according to renal function. Of note, little diffusion of this molecule to the gut lumen has been observed, possibly accounting for its low propensity to select for Clostridioides difficile [5].

In a phase III trial in patients with HABP, ceftobiprole monotherapy was as efficacious as the combination of ceftazidime and linezolid in terms of both clinical and microbiological cure and was noninferior to ceftazidime/linezolid in the subgroup of patients with HABP, but excluding VABP. Ceftobiprole and ceftazidime/linezolid were similarly well tolerated. Based on current evidence, Ceftobiprole is an efficacious and well-tolerated option for empirical treatment of patients with HABP (excluding VABP) [6].

investigated the in vitro susceptibility of ceftobiprole and its potential synergistic activity in combination with other antimicrobials against 46 selected Gram-positive pathogens displaying resistance or decrease susceptibility to several drugs. The gradient-cross method was used to assess synergism between ceftobiprole and daptomycin, levofloxacin, linezolid, rifampicin, and piperacillin/tazobactam. In conclusion, ceftobiprole exhibited a potent in vitro antibacterial activity and good synergy with daptomycin against a range of tested Gram-positive isolates, despite their antibiotic resistance phenotypes. The use of ceftobiprole alone or in combination may therefore provide a promising alternative therapy for the treatment of infections caused by resistant Gram-positive bacteria [7].

Ceftaroline is another fifth-generation cephalosporin approved for the treatment of CAP and acute bacterial skin and skin structure infections (ABSSSIs). It recently received an additional approval for the treatment of S. aureus bacteremia (SAB) associated with ABSSSIs. Ceftaroline has shown efficacy for the treatment of methicillin-resistant SAB, including for isolates with elevated minimum inhibitory concentrations to conventional therapy, when used alone or in combination with other agents. In multiple studies, ceftaroline displayed rapid bloodstream eradication, even in the setting of refractory MRSA SAB or infective endocarditis [4][8].

It has activity against MDR Gram-positive bacteria, including MRSA, VRSA (vancomycin-resistant S. aureus), and respiratory pathogens such as S. pneumoniae (including multi-drug-resistant strains), Haemophilus influenzae, and Moraxella catarrhalis. Mirroring other broad-spectrum cephalosporins, ceftaroline does not possess activity against extensively resistant Gram-negative bacilli and exhibits limited activity against most nonfermentative Gram-negative bacilli (e.g., P. aeruginosa, Acinetobacter spp.) as well as many anaerobic species [9].

The recommended duration of treatment is 5–14 days for cSSTI and 5–7 days for CAP, and the standard dose in adults with normal renal function is 600 mg by 1 h intravenous infusion every 12 h. In adults with a creatinine clearance <50 mL/min, ceftaroline dose should be reduced. If the creatinine clearance is between 30 and 50, the recommended dose is 400 mg every 12 h; if the creatinine clearance is between 15 and 30 mL/min, the recommended dose is 300 mg every 12 h; and if creatinine clearance is less than 15 mL/min, the recommended dose is 200 mg every 12 h [10].

The most common adverse reactions reported in ≥3% of approximately 3242 patients treated in clinical trials were diarrhea, headache, nausea, pruritus, and were generally mild or moderate in severity. Diseases associated with C. difficile (diarrhea) can be observed. In addition, ceftaroline lowers the epileptogenic threshold [11].

In phase 3, multicenter, randomized, and double-blind studies, Corey at al. evaluated the safety and efficacy of ceftaroline in a comparative fashion. Noninferiority was observed, and satisfactory clinical cure rates were achieved by ceftaroline (600 mg every 12 h) compared to vancomycin plus aztreonam (1 g each every 12 h) for 5–14 days in complicated skin and skin-structure infections [12].

Dalbavancin is a lipoglycopeptide approved in US and Europe for the treatment of ABSSIs caused by Gram-positive bacteria. Like other members of its family (telavancin and oritavancin, not yet widely approved), dalbavancin is an analogue of glycopeptides incorporating structural modifications responsible for novel and somehow improved pharmacokinetic and pharmacodynamic features [4][13]. Lipoglycopeptides act by blocking cell wall synthesis and binding to the D-Ala-D-Ala terminus of the pentapeptide peptidoglycan precursors; in addition, they anchor to the cell wall with high affinity thanks to their lipophilic lateral chain. Moreover, the addition of a lateral lipophilic chain gives dalbavancin a unique pharmacokinetic profile, with a very long half-life (>10 days)

Dalbavancin has in vitro activity against sensible and MDR Gram-positive bacteria, including MRSA, methicillin-resistant coagulase negative staphylococci and VRE, with the exception of those with a vanA phenotype.

It can be administered in two ways: either as a single IV dose of 1500 mg over 30 min, or as a two-dose regimen, with an initial 1000 mg IV dose over 30 min, followed by 500 mg one week later. Dose adjustments are required only for patients with severe renal dysfunction (CrCl < 30 mL/min) It shows a high bone penetration and a favorable safety profile when administered weekly up to 8 weeks.

The unique pharmacokinetic profile of dalbavancin allows treatment of MDR infections with a once or twice weekly administration, thus avoiding hospitalization or decreasing length of hospital stay and overall general costs and decreasing all the risks connected to long-term indwelling venous catheters that are needed for other daily administered antibiotics (such as daptomycin). Dalbavancin appears specifically ideal for treatment in an outpatient setting. Bouza et al. reported an overall clinical success rate of 84.1% with dalbavancin when treating ABSSIs, osteomyelitis, prosthetic joint infections, and catheter-related bacteremia, with an average cost reduction of 3064 € per patient [14].

In a recent meta-analysis including 7 RCTs and 2665 patients, Y. Wang et al. showed that dalbavancin was comparable to other antibiotics in treating chronic Gram-positive infections in terms of efficacy and safety, and that the dual-dose regimen showed a better safety profile compared with the single-dose regimen in the treatment of ABSSSIs. Specifically, clinical response to dalbavancin was better in catheter-related bloodstream infections (CRBSIs) and osteomyelitis, but no significant difference was observed in terms of adverse events between dalbavancin and other treatments [15].

Tedizolid phosphate is a newer oxazolidinone prodrug that is rapidly converted in its microbiologically active counterpart, tedizolid, by endogenous phosphatases [16]. Similar to linezolid, it inhibits bacterial protein synthesis binding to 23S-rRNA of the bacterial ribosomal subunit 50S. Moreover, tedizolid overcomes the most important mechanism of resistance to linezolid, which is the methylation of the 23S rRNA subunit by the enzyme cfr [17].

(including vancomycin-resistant strains), Staphylococcus spp. Its in vitro activity against these bacteria is 4–8 times greater than linezolid, meaning that it can be used at lower doses [18]. Tedizolid is indicated in the treatment of ABSSSIs caused by Gram-positive bacteria, even if resistant to glycopeptides, daptomycin, and linezolid. It can be administered orally or intravenously at the same dosage (200 mg once daily), since its oral bioavailability is almost complete.

In the randomized, double-blind, phase 3, noninferiority ESTABLISH-2 trial, tedizolid (200 mg once daily for 6 days) was found to be noninferior in efficacy to linezolid (600 mg twice-daily for 10 days) for the treatment of ABSSSIs and to be similarly tolerated, but with a lower incidence of gastrointestinal AEs and bone marrow suppression than linezolid [19].

Fosfomycin disodium is a recently redeveloped formulation of an old cell wall active agent. Entry is achieved through transport systems utilized by alpha glycerol-phosphate and glucose-6-phosphate, key elements of the bacterial metabolism; this explains the often reduced fitness and virulence of fosfomycin-resistant bacterial strains [20]. Fosfomycin inhibits an early step of the peptidoglycan synthesis, blocking formation of the N-acetylmuramic acid, thus acting in direct synergism with β-lactams. Fosfomycin is active in the log-phase of bacterial growth and exerts bactericidal effects against a broad spectrum of pathogenic bacteria, including Gram-positive (e.g., S. aureus and E. faecalis) and Gram-negative bacteria (e.g., E. coli and Klebsiella spp.).

Fosfomycin disodium reaches high serum concentrations when dosed at 4 g every 6 h intravenously. However, when used as monotherapy, rapid onset of resistance to fosfomycin is observed. These features strongly support the need to always combine fosfomycin with other antimicrobials, including β-lactams, aminoglycosides, daptomycin, and newer molecules such as ceftaroline, ceftobiprole, and ceftazidime-avibactam. However, long courses of high-dose fosfomycin disodium are associated with significant sodium and water retention, which may be difficult to manage in patients with concurrent decompensated heart failure, renal failure, or liver cirrhosis [20].

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