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Ceftaroline, Linezolid, Daptomycin, Tigecycline are disadvantages of such new generation antibiotics

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Annotation: Microbial resistance has reached alarming levels, threatening to outpace the ability to counter with more potent antimicrobial agents. In particular, methicillin-resistant Staphylococcus aureus (MRSA) has become a leading cause of skin and soft-tissue infections and PVL-positive strains have been associated with necrotizing pneumonia. Increasing reports of growing resistance to glycopeptides have been noted, further limiting the efficacy of standard antibiotics, such as vancomycin

Key words: Ceftaroline, antibiotic, cephalosporin, methicillin-resistant Staphylococcus aureus, MRSA, multidrug resistant organisms

Microbial pathogens have an extraordinary capacity to develop resistance to antimicrobial agents. Within the last two decades, resistance has escalated, occasionally at seemingly exponential rates, threatening to outpace the ability to counter with more potent antimicrobial agents. Methicillin-resistant Staphylococcus aureus (MRSA), first isolated in the 1960s, became a prominent nosocomial pathogen over the past three decades. The advent of community-associated MRSA (CA-MRSA), which arose de novo outside the healthcare environment, has dramatically heightened the importance of MRSA. Today, MRSA is the leading cause of community-acquired skin and soft tissue infections (SSTI) and a cause of necrotizing pneumonia.1,2 The dramatic escalation in MRSA, which is now globally ubiquitous, coupled to intrinsic resistance to many of the existing antimicrobial agents, renders this an enormous public health issue. MRSA has also recently exhibited an inexorable creep in minimum inhibitory concentrations (MIC) to the standard intravenous antibiotic (vancomycin) utilized in its management. In addition, S. aureus strains with vancomycin-intermediate resistance (VISA), heteroresistance (hVISA), and vancomycin resistance (VRSA) have been described.3 These resistant strains are associated with increased morbidity and mortality above that of methicillin-sensitive Staphylococcus aureus (MSSA), and often require surgical intervention coupled to a sparse selection of suitable antimicrobial therapy.

Fortunately, alternatives to vancomycin have been developed in the past decade for the treatment of multidrug resistant (MDR) Gram-positive bacterial infections including an oxazolidinone (linezolid), a lipopeptide (daptomycin), a streptogramin (quinupristin-dalfopristin), and a glycylcycline (tigecycline).5,6 Telavancin is a recent addition to the Gram-positive arsenal, and is a lipoglycopeptide which inhibits both bacterial cell wall synthesis and cell-membrane function.7

Despite these novel agents, resistance continues to evolve, and strains resistant to linezolid, quinupristin/dalfopristin and daptomycin have been described. Moreover, there are disadvantages associated with these contemporary antibiotic classes. For example, linezolid has

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minimal Gram-negative activity (due to efflux pumps), although it does have some activity against anaerobes and Mycobacteria spp. Furthermore, linezolid is bacteriostatic and its long-term use (e.g., >2 weeks) has been associated with the development of peripheral neuropathy, lactic acidosis, and thrombocytopenia (as well as the potential for trilineage bone marrow suppression). Daptomycin lacks pulmonary activity, and may cause a pulmonary hypersensitivity reaction and myopathy. Additionally, daptomycin resistance has been noted in the setting of prior vancomycin therapy, especially with suboptimal dosing and sequestered infections including osteomyelitis, endocarditis, and device related infections

Ceftaroline is the bioactive metabolite of ceftaroline fosamil, an N-phosphonoamino water-soluble cephalosporin prodrug, which is rapidly converted in vivo upon the hydrolysis of the phosphonate group by plasma phosphatises. Ceftaroline's chemical stability and water solubility is attributed in part from improved crystallization and hygroscopicity imparted by innovated chemical modifications, necessitating administration as a prodrug via intravenous or intramuscular routes. Ceftaroline has 16-fold greater activity than ceftriaxone against MSSA isolates. For example, ceftaroline's MIC90 is consistently reported to be 0.25 μg/ml (≤0.03–1 μg/ml) for MSSA, compared with 4 μg/ml for ceftriaxone, 1 μg/ml for vancomycin, and ≤0.12 μg/ml for imipenem. Ceftaroline demonstrated up to four-fold greater activity than vancomycin against MRSA isolates, independent of the isolate's source (blood, skin, or respiratory tract), demonstrating MIC and MBC values ranging between 0.125 to 2 μg/ml and 0.5 to 2 μg/ml for ceftaroline and vancomycin, respectively. As expected, ceftaroline was ≥8-fold more potent than cefepime and ≥16-fold more active than ceftriaxone against MRSA strains. Ceftaroline MIC90 values against MRSA were 0.5–2 μg/ml, similar to that of linezolid and vancomycin (MIC90 of 1–2 μg/ml).49 Moreover, the MBC against MRSA strains were 1, 2, and >64 μg/ml, respectively, for ceftaroline, vancomycin, and linezolid.

Ceftaroline's superiority over vancomycin was evident in hVISA, VISA, and VRSA as well as MRSA strains concomitantly resistant to linezolid and daptomycin. The MICs and MBCs for hVISA strains (n=100 isolates) were 2 (0.25–4 μg/ml) and 2 μg/ml, respectively, for ceftaroline. The corresponding MICs and MBCs were 4 and 8 μg/ml, respectively, for vancomycin and 1 and 16 μg/ml, respectively, for linezolid. Ceftaroline yielded MICs of 1–4 μg/ml against both linezolid-sensitive and -resistant S. aureus isolates. Additionally, ceftaroline exhibited bactericidal effects, as opposed to the slowly bactericidal activity exhibited by vancomycin and the bacteriostatic activity of linezolid, and has synergy in combination with tobramycin. Finally, ceftaroline's MIC values against quinupristin-dalfopristin-resistant strains were similar in activity to that described for MRSA (MIC50 and MIC90, 1 μg/ml). Ceftaroline is also active against coagulase-negative Staphylococcus epidermidis (CoNS). Ceftaroline exhibited MIC90 of 0.12 (0.06–0.12) and 0.5 (0.25–2.0) μg/ml for oxacillin-susceptible and oxacillin-resistant isolates of CoNS, respectively. Ceftaroline demonstrated MICs of ≤0.016 to 2 μg/ml against CoNS strains having reduced susceptibility to vancomycin (MIC of 4 μg/ml).21 Ceftaroline was also active against quinupristin-dalfopristin- and linezolid-nonsusceptible isolates (MIC90, 1.0 μg/ml and 0.5 μg/ml), respectively.

Based on clinical trial data to date, ceftaroline appears to be safe and well-tolerated. Since

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ceftaroline is a cephalosporin, it has caused serious hypersensitivity reactions in patients who are allergic to cephalosporins and among some patients with penicillin allergies. Hence, a careful history of prior antibiotic allergies should be obtained prior to the use of ceftaroline. Ceftaroline is a novel, broad-spectrum cephalosporin, which exhibits bactericidal activity against Gram-positive bacteria, including MRSA and MDRSP. Ceftaroline offers an exciting addition to the anti-MRSA armamentarium, including activity against VISA, hVISA, VRSA, and daptomycin- and linezolid-resistant strains. Unique among many anti-MRSA agents, ceftaroline additionally provides activity against Gram-negative respiratory pathogens is not effective against organisms with AmpC- or ESBLs, research investigating combination with β-lactamase inhibitors to provide potential activity against these Gram-negative organisms are underway. To date, ceftaroline has demonstrated an excellent safety profile comparable to contemporary cephalosporins and exhibits an inherently low propensity to inducing resistance, especially among Gram-positive organisms; however, long-term data and clinical experience with this novel agent are needed.

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