New Antimicrobial Agents for the Treatment of Staphylococcal Infections in Children

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KEYWORDS

• *Staphylococcus aureus* • MRSA • Vancomycin • Ceftaroline • Daptomycin • Dalbavancin • Telavancin • Tedizolid

KEY POINTS

- Decreased susceptibility of methicillin-resistant *Staphylococcus aureus* (MRSA) to vancomycin is increasing and associated with treatment failure, even when MRSA strains are fully susceptible to vancomycin.
- Treatment with vancomycin requires careful monitoring of drug levels because there is a potential for nephrotoxicity.
- In the last few years several new antimicrobial agents—daptomycin, ceftaroline, telavancin, dalbavancin, and tedizolid—have been approved for treatment staphylococcal infections, including MRSA, in adults.
- Ceftaroline and daptomycin have been approved for use in children.
- Ceftaroline, the first beta-lactam antibiotic with activity against MRSA, has been approved for treatment of community-acquired bacterial pneumonia and complicated skin and skin structure infections.

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INTRODUCTION

Staphylococcus aureus was first identified as bacterial pathogens in the 19th century. Penicillins were considered the drug of choice until *S aureus* developed penicillin resistance by production of beta-lactamase. This led to discovery of semisynthetic penicillins such as dicloxacillin and nafcillin but quickly methicillin-resistant *S aureus* (MRSA) emerged owing to the acquisition of genes that have decreased affinity for beta-lactams, including antistaphylococcal penicillins, cephalosporins, and carbapenems.[1] In the last 50 years, vancomycin has been the agent of choice to treat MRSA infections, although other agents such as clindamycin, tetracyclines, and cotrimoxazole have also been used. However, vancomycin treatment failure is not uncommon, even when MRSA strains are fully susceptible to vancomycin (minimum inhibitory concentration [MIC] $\leq$ 2 mg/mL).[2] Treatment with vancomycin requires careful monitoring of drug levels because there is a potential for nephrotoxicity. In addition, resistance to clindamycin is not infrequent, which also limits therapeutic options for treating infections owing to MRSA in children. In the last few years, tedizolid, daptomycin, telavancin, dalbavancin, and ceftaroline have been approved for the treatment of staphylococcal infections, including MRSA, in adults. Ceftaroline and daptomycin have been approved by the US Food and Drug Administration (FDA) for use in children. Ceftaroline, daptomycin, dalbavancin, telavancin, and tedizolid offer a number of advantages over currently available drugs to treat staphylococcal and other Gram-positive infections, especially vancomycin, including improved antimicrobial activity; superior pharmacokinetics, pharmacodynamics, tolerability, and dosing, including once-daily and weekly regimens; and less need for monitoring drug levels.

CEFTAROLINE

Chemistry and Pharmacology

Cephalosporins are beta-lactam antibiotics derived from the fungus *Cephalosporium* (now called *Acremonium*). There are numerous agents in this class, each containing a beta-lactam ring fused to a 6-member dihydrothiazine ring, and 2 side chains that can be modified to affect antibacterial activity and pharmacokinetic properties.[3] Ceftaroline fosamil is water soluble, an *N*-phosphono type prodrug of a cephalosporin class of beta-lactam antibacterial drugs, rapidly converted to the active form, ceftaroline.[4] Ceftaroline was synthesized with specific manipulations of the side chains to provide enhanced activity against MRSA and multidrug-resistant *Streptococcus pneumoniae* isolates, making it the first available beta-lactam with this ability.[5] One of the mechanisms of resistance to beta-lactam agents is through mutations of the penicillin-binding proteins (PBP). MRSA and penicillin-resistant *S pneumoniae* produce PBP2a and PBP-2x variants, respectively.[6]

Similar to other cephalosporins, ceftaroline binds to PBPs, inhibiting transpeptidation. This interaction blocks the final stage of peptidoglycan synthesis and inhibits bacterial cell wall synthesis, ceftaroline binds to PBP 1 to 4 and has a high affinity to PBP2a, the protein responsible for conferring methicillin resistance in *S aureus*.[6] Ceftaroline also has activity against penicillin-resistant *S pneumoniae* owing to binding affinity to PBP2x.[6]

Pharmacokinetics and Pharmacodynamics

Limited pharmacokinetic studies on ceftaroline exist for pediatric patients. In a phase I open-label, noncomparative study, a single dose was examined for pharmacokinetics in 9 subjects aged 12 to 17 years.[7] A single 1-hour infusion of ceftaroline 8 mg/kg was administered to hospitalized patients for suspected infection who weighed less than 75 kg or 600 mg for subjects who weighed 75 kg or more. Patients were excluded if