New Antibiotics Mainly Against Resistant Gram-Positives

Robin Patel
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Ceftaroline

Ceftaroline fosamil is the first “fifth generation” cephalosporin to be approved by the United States Food and Drug Administration (FDA); it is unique in its activity against methicillin-resistant Staphylococcus aureus (MRSA) (1). As with other β-lactams, it binds to penicillin-binding proteins (PBPs), inhibiting cell wall biosynthesis. However, compared to other FDA-approved β-lactams, it has high affinity for PBP2a, the mecA gene product of methicillin-resistant staphylococci. Its spectrum is most like ceftriaxone, but with additional activity against methicillin-resistant staphylococci as well as cephalosporin-resistant isolates of Streptococcus pneumoniae. It has activity against vancomycin-intermediate S. aureus (VISA) and hetero-VISA as well as non-extended-spectrum β-lactamase (ESBL)-producing Escherichia coli, Klebsiella pneumoniae, Citrobacter freundii and Enterobacter cloacae. It does not have clinically useful activity against enterococci or Pseudomonas aeruginosa.

Adverse reactions include diarrhea, nausea, and rash.

Two clinical trials of complicated skin and skin structure infection compared ceftaroline 600 mg every 12 hours to vancomycin plus aztreonam, 1 g of each every 12 hours, for 5 to 14 days (4). Patients with diabetic foot ulcers, decubiti, extensive burns, or known or suspected Pseudomonas infection were excluded. In the clinically evaluable population, clinical cure rates were 92 and 93% with ceftaroline and vancomycin, respectively.

Ceftobiprole is another “fifth generation” cephalosporin with high affinity for PBP2a, and consequent activity against methicillin-resistant staphylococci (5). Because of low water solubility, it is administered intravenously as a prodrug, ceftobiprole medocaril. It is not approved by the United States FDA.

Telavancin

Telavancin is a lipoglycopeptide derivative of vancomycin that possesses a decylaminoethyl side chain appended to the vancosamine sugar and a phosphonomethyl aminomethyl group (10). It has a dual mechanism of action. Like vancomycin, it binds to the peptidoglycan precursor at the D-Ala-D-Ala terminus; the decylaminoethyl side chain provides improved binding affinity for D-Ala-D-Ala (10). Unlike vancomycin, telavancin triggers concentration-dependent cell depolarization which results in leakage of cytoplasmic ATP and K+. Telavancin is active against staphylococci, including methicillin-resistant strains, as well as VISA and hetero-VISA. Telavancin is also active against Streptococcus pyogenes, Streptococcus agalactiae, and S. pneumoniae. It does not have clinically useful activity against VanA vancomycin-resistant enterococci.

Telavancin is associated with altered taste, nausea, vomiting, foamy urine, nephrotoxicity, constipation, QT prolongation, and the infusion-related red-person syndrome (10). Its pregnancy category is C.

Two clinical trials of complicated skin and skin structure infections compared telavancin 10 mg/kg per day to vancomycin 1 g every 12 h (11). In the clinically evaluable population, at 7 to 14 days after receipt of the last antibiotic dose, success was achieved in 88 and 87% of patients who received telavancin and vancomycin, respectively.

Tigecycline

Tigecycline is an expanded-spectrum glycylcycline that inhibits protein synthesis by binding to the 30S ribosomal subunit, blocking entry of aminoacyl-tRNA molecules. Tigecycline overcomes two tetracycline resistance mechanisms, ribosomal protection and efflux pumps. Tigecycline has in vitro activity against staphylococci, including MRSA and VISA, penicillin-resistant S. pneumoniae and vancomycin-resistant enterococci. Tigecycline is also active against Acinetobacter baumannii, Stenotrophomonas maltophilia, and most Enterobacteriaceae (including...
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some ESBL-producing strains). It does not have clinically useful activity against \textit{P. aeruginosa}. Two clinical trials of complicated skin and skin structure infections compared tigecycline 100 mg once and then 50 mg q12h with vancomycin 1 g q12h plus aztreonam 2 g q12h for 5 to 14 days (6). In the clinically evaluable population, clinical cure rates were 87 and 89% for tigecycline and vancomycin plus aztreonam, respectively.

Two clinical trials of complicated intra-abdominal infection compared tigecycline 100 mg once and then 50 mg q12h with imipenem/cilastatin 500 mg q6h for 5 to 14 days (3). In the clinically evaluable population, the clinical cure rates were 87% for both tigecycline and imipenem.

Two clinical trials of hospitalized patients with community-acquired pneumonia compared tigecycline 100 mg once, and then 50 mg q12h with levofloxacin 500 mg q12h (12). In the clinically evaluable population, the clinical cure rates were 90 and 86% for tigecycline and levofloxacin, respectively.

**Daptomycin**

Daptomycin is a cyclic lipopeptide that binds to the bacterial plasma membrane, causing membrane depolarization and release of intracellular ions, ultimately leading to cell death. Its activity includes methicillin-resistant staphylococci, VISA, penicillin-resistant \textit{S. pneumoniae}, and vancomycin-resistant enterococci.

Adverse effects include gastrointestinal side effects, injection site reactions, fever, headache, insomnia, dizziness, rash, and increase in creatine phosphokinase.

Two clinical trials of complicated skin and skin structure infections compared daptomycin 4 mg/ kg q24h with vancomycin 1 g q12h or penicillinase-resistant penicillins 4 to 12 g per day (2). In the clinically evaluable population, the clinical success rates were 83 and 84% for daptomycin and the comparators, respectively.

Daptomycin is also approved by the United States FDA for the treatment of \textit{S. aureus} bacteremia, including right-sided endocarditis, caused by methicillin-susceptible \textit{S. aureus} and MRSA (8).

**References**

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