Cephalosporins

Cephalosporins are beta-lactam antimicrobials used to manage a wide range of infections from gram-positive and gram-negative bacteria. The five generations of cephalosporins are useful against skin infection, resistant bacteria, meningitis, and other infections.

Indications

Cephalosporins are antimicrobials grouped into five generations based on their spectrum of coverage against gram-positive and gram-negative bacteria and their temporal discovery.

First-generation cephalosporins have coverage against most gram-positive cocci as well as some gram-negative bacteria, e.g., *Escherichia coli (E. coli), Proteus mirabilis,* and *Klebsiella pneumoniae*. Second-generation cephalosporins have coverage against *Haemophilus influenzae (H. influenzae), Moraxella catarrhalis,* and *Bacteroides spp.* Third-generation cephalosporins have less coverage against most gram-positive organisms but have increased coverage against Enterobacteriaceae, *Neisseria spp.,* and *H. influenzae*. Fourth-generation cephalosporins have similar coverage as third-generation cephalosporins but with additional coverage against gram-negative bacteria with antimicrobial resistance, e.g., beta-lactamase. Fifth-generation cephalosporins have coverage against methicillin-resistant staphylococci and penicillin-resistant pneumococci.

First-generation cephalosporins include cefazolin, cephalothin, cephapirin, cephradine, cefadroxil, and cephalexin. First-generation cephalosporins have active coverage against most gram-positive cocci, such as *staphylococci spp.* and *streptococci spp.,* while having minimal coverage against gram-negative bacteria. Gram-negative bacteria that are more susceptible to first-generation cephalosporins are *Proteus mirabilis, E. coli,* and *Klebsiella pneumoniae*. Oral first-generation cephalosporins are commonly prescribed to use against uncomplicated skin and soft tissue infections such as cellulitis and abscesses commonly due to a S*taphylococci spp.* or S*treptococci spp.* infection. Additionally, clinicians can use them for bone, respiratory tract, genitourinary tract, biliary tract, bloodstream infection, otitis media, and surgical prophylaxis. In fact, cefazolin is the cephalosporin of choice for surgical prophylaxis. One of the non-FDA-approved indications is to use first-generation cephalosporins for endocarditis prophylaxis for those who are susceptible and undergoing a dental or respiratory procedure.

Second-generation cephalosporins divide into two subgroups: the second-generation and the cephamycin subgroup. Some of the second-generation subgroups include cefuroxime and cefprozil. The cephamycin subgroup includes cefmetazole, cefotetan, and cefoxitin. Within the first subgroup, cefuroxime has increased coverage against *H. influenzae*. Indications for cefuroxime also include Lyme disease in pregnant women and children. The cephamycin subgroup has increased coverage against *Bacteroides* species. Second-generation cephalosporins have less activity against gram-positive cocci than first-generation cephalosporins but have increased activity against gram-negative bacilli. They are often prescribed to treat respiratory infections such as bronchiolitis or pneumonia. Other indications for second-generation cephalosporins are similar to first-generation indications (bone, respiratory tract, genitourinary tract, biliary tract, bloodstream infection, otitis media, and surgical prophylaxis). In addition to the gram-negative bacteria covered by first-generation

cephalosporins, second-generation cephalosporins also have coverage against *H. influenzae, Enterobacter aerogenes, Neisseria* species, and *Serratia marcescens*.

Third-generation cephalosporins include cefotaxime, ceftazidime, cefdinir, ceftriaxone, cefpodoxime, cefoperazone, and cefixime. This generation has extended gram-negative bacteria coverage often used to treat gram-negative infections resistant to the first and second generation or other beta-lactam antimicrobials. When given IV, third-generation can penetrate the blood-brain barrier and cover bacteria in the cerebral spinal fluid, especially ceftriaxone and cefotaxime. Ceftriaxone can be given to treat meningitis caused by *H. influenzae*, *Neisseria meningitidis*, or *Streptococcus pneumoniae.* Ceftriaxone is also used to treat gonorrhea and disseminated Lyme disease. Ceftazidime, very importantly, has *Pseudomonas aeruginosa* coverage.

Fourth-generation cephalosporin includes cefepime. Cefepime is a broad-spectrum antimicrobial that can penetrate the cerebral spinal fluid. Cefepime has an additional quaternary ammonium group, allowing them to better penetrate the outer membrane of gram-negative bacteria. Similar to the activity of cefotaxime and ceftriaxone, cefepime can cover *Streptococcus pneumoniae* and methicillin-sensitive *Staphylococcus aureus* (MSSA). Similar to ceftazidime, cefepime, very importantly, can cover for *Pseudomonas aeruginosa.* In addition to the gram-negative bacteria that third-generation covers (*Neisseria spp.*, *H. influenzae*, and Enterobacteriaceae), cefepime can provide coverage against beta-lactamase-producing gram-negative bacilli. Although effective against both gram-positive and gram-negative bacteria, cefepime is reserved for serious systemic infection in patients who are likely to have multi-resistance organisms.

Fifth-generation cephalosporins include ceftaroline. Ceftaroline is also a broad-spectrum antimicrobial and thus can cover susceptible gram-positive and gram-negative organisms. However, what makes it unique from the rest of the cephalosporins is that it has coverage against methicillin-resistant *Staphylococcus aureus* (MRSA). Ceftaroline can also cover *Listeria monocytogenes* and *Enterococcus faecalis*. However, ceftaroline does not cover *Pseudomonas aeruginosa*.

Mechanism of Action

Bacteria synthesize a cell wall that is strengthened by cross-linking peptidoglycan units via penicillin-binding proteins (PBP, peptidoglycan transpeptidase). Initially derived from the fungus *Cephalosporium sp.*, cephalosporins are a large group of bactericidal antimicrobials that work via their beta-lactam rings. The beta-lactam rings bind to the penicillin-binding protein and inhibit its normal activity. Unable to synthesize a cell wall, the bacteria die.

Staphylococcus aureus, which is initially susceptible to cephalosporins, can develop resistance by changing the structure of the penicillin-binding proteins. *S. aureus* does this by having a gene that encodes a modified penicillin-binding protein; this prevents the cephalosporin's beta-lactam rings from inactivating the protein. The bacterium that develops this mechanism of resistance is called methicillin-resistant *Staphylococcus aureus* (MRSA). As indicated above, out of the five generations of cephalosporin, only the fifth generation ceftaroline has coverage against methicillin-resistant *Staphylococcus aureus*. Another crucial resistance mechanism is producing the enzyme beta-lactamase, which cleaves the beta-lactam ring, preventing it from

attaching to the penicillin-binding proteins, e.g., peptidoglycan transpeptidase. Beta-lactamase inhibitors can be co-formulated with cephalosporins to increase their spectrum of activity, e.g., ceftazidime/avibactam and ceftolozane/tazobactam.