

The new fifth-generation cephalosporins – a balance between safety and efficacy

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ABSTRACT

Cephalosporins are beta-lactam antibiotics classified into five generations. The newest generation has three representatives: ceftaroline fosamil, the combination ceftolozane/tazobactam (cephalosporin/beta-lactamase inhibitor), and ceftobiprole medocartil. These new cephalosporins are valuable anti-infective agents, with potent activity against multidrug-resistant bacteria, and with a positive balance between benefits and side effects. However, the fifth-generation cephalosporins should be judiciously used to prevent the occurrence of bacterial resistance phenomenon.

Keywords: cephalosporins, ceftaroline, ceftolozane, ceftobiprole, MRSA, community-acquired pneumonia, complicated skin and soft tissue infections



INTRODUCTION

Cephalosporins (CFs) are beta-lactam antibiotics with numerous representatives widely used in the therapy of infectious diseases. Like other beta-lactam antibiotics, CFs inhibit the synthesis of the bacterial cell wall. The beta-lactam ring is essential in binding to the penicillin-binding proteins, crucial enzymes in the synthesis of the bacterial cell wall. The high affinity of fifth-generation CFs for penicillin-binding proteins leads to an efficient activity against clinically relevant pathogens. The new CFs (fourth and fifth generations) have

emerged as a result of increased bacterial resistance to classical antibiotics. Based on the antimicrobial activity, the CFs are classified into five generations (Table 1) [1]. Representatives of the fifth-generation which are used in therapy are comprised of: ceftaroline fosamil, ceftolozane/tazobactam, and ceftobiprole medocartil [1-3]. The clinical studies conducted so far support the positive balance between benefits and side effects for these new CFs. However, the fifth-generation CFs should be judiciously used in difficult-to-treat bacterial infections

only, in the situation where other antibacterial drugs were not efficient.

REPRESENTATIVES

Ceftaroline fosamil

Ceftaroline fosamil (anatomical therapeutic chemical (ATC) code: J01DI02) is a relatively recent approved cephalosporin from the fifth-generation [1,4,5]. The U.S. Food and Drug Administration approved ceftaroline fosamil in 2010 and the European Medicine Agency, in 2011 (under trade name Teflaro and Zinforo) [5-7]. Ceftaroline fosamil is active against

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Gram-positive (G(+)) organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus pneumoniae*, as well as common Gram-negative (G(-)) organisms [6].

Physical-chemical properties.

Ceftaroline is an oxyimino compound based on the structure of cefozopran (a fourth-generation representative) [6]. Ceftaroline fosamil is a prodrug that turns *in vivo* into ceftaroline (the active metabolite). The name „fosamil” is given by an extra phosphono group in the chemical structure comparative to ceftaroline. The resulted compound has the advantage that it is more water-soluble [6]. The oxime group in the C7 acyl moiety and a 1,3-thiazole ring attached to the central nucleus (C3 position) facilitate the increased activity against MRSA (Table 2) [6,8]. The parenteral formulation (600 mg powder for concentrate for solution for infusion) contains an equivalent amount of ceftaroline fosamil acetic acid solvate monohydrate [5].

Indications, dosing and

administration. Ceftaroline fosamil has been approved for administration to children (neonates, infants, children, adolescents) for the same indications as for adults: complicated skin and soft tissue infections and community-acquired pneumonia [5]. Ceftaroline fosamil is administered intravenously (600 mg every 12 hours over 1 hour in adults) during 5-14 days. Dosage adjustment is necessary for patients with moderate to severe renal impairment [6]. Also, ceftaroline fosamil is used *off-label* in the treatment of bacteremia, endocarditis, osteoarticular infections, hospital-acquired pneumonia, and meningitis [9].

Safety of ceftaroline fosamil.

Ceftaroline fosamil is considered effective in therapy, and well-tolerated, with a good safety profile. However, ceftaroline fosamil could be responsible for diarrhea, nausea, headache and pruritus as the most common side effects with similar rates compared to other antibiotics [5,6,9-11]. Precautions for use and special warnings are for hypersensitivity reactions, *Clostridium difficile*-associated diarrhea, superinfections with non-susceptible bacteria, and pre-existing seizure disorder. Ceftaroline fosamil has a low potential for drug-drug interactions [6,12]. Because the effects of the compound in pregnancy and lactation or on fertility are unknown, it is advisable to avoid the treatment in these situations [5]. More studies are needed in the future to assess the safety profile of ceftaroline fosamil [9].

Ceftolozane/tazobactam combination

Ceftolozane is a new fifth-generation CF, a derivative of ceftazidime (third generation). Because it is not resistant to beta-lactamases, ceftolozane was combined with an inhibitor of beta-lactamases, respectively tazobactam. The obtained combination provides great activity against extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and certain anaerobic germs [2,13]. The combination of ceftolozane with tazobactam (ATC code: J01DI54) was approved in 2014 by the FDA, and in 2015 by the EMA (under trade name Zerbaxa). Recently, the FDA has approved Zerbaxa for the treatment of adults with hospital-acquired and ventilator-associated bacterial pneumonia [14-16].

TABLE 1. Classification of the most used CFs by generation and route of administration (G(+) = Gram positive, G(-) = Gram negative) [1,2,17,22,24].

Generations/Administration									
First		Second		Third		Fourth		Fifth	
Cefalotine	parenteral	Cefamandol	parenteral	Cefotaxime	parenteral	Cefpirome	parenteral	Ceftaroline fosamil	parenteral
Cefapirine	parenteral	Cefuroxime	parenteral	Ceftazidime	parenteral	Cefepime	parenteral	Ceftolozane/tazobactam	parenteral
Cefalexina	oral	Cefoxitin	parenteral	Ceftriaxone	parenteral			Ceftobiprol medocaril	parenteral
Cefadroxil	oral	Cefotetan	parenteral	Cefoperazone	parenteral				
Cefatrizine	oral	Cefaclor	oral	Flomoxef	parenteral				
Cefradine	oral	Cefprozil	oral	Cefixime	oral				
		Cefuroxime axetil	oral	Ceftibuten	oral				
Antibacterial spectrum									
G(+) cocci (<i>staphylococci spp.</i> and <i>streptococci spp.</i>) All have minimal activity against G(-) bacteria.		All have less activity against G(+) cocci and increased activity against G(-) bacilli compared to the first-generation. Cefuroxime has increased activity against <i>Haemophilus influenza</i> . Cefotetan and cefoxitin have increased activity against <i>Bacteroides spp.</i>		All have extended activity against G(-) bacteria (including those resistant to the first and second generation CFs or other beta-lactam antibiotics). Ceftriaxone is useful in the treatment of meningitis (caused by <i>Haemophilus influenza</i> , <i>Neisseria meningitidis</i> , or <i>Streptococcus pneumoniae</i>) gonorrhea and disseminated Lyme disease. Ceftazidime presents activity against <i>Pseudomonas aeruginosa</i> .		Cefepime is active against <i>Streptococcus pneumoniae</i> , methicillin-resistant <i>Staphylococcus aureus</i> (MRSA), and <i>Pseudomonas aeruginosa</i> . In addition to the activity of the third generation, cefepime has activity against beta-lactamase-producing G(-) bacilli. Cefepime is reserved for severe systemic infections produced by multi-resistant organisms.		Ceftaroline is a broad-spectrum antibiotic with great activity against MRSA, <i>Listeria monocytogenes</i> , <i>Enterococcus faecalis</i> , and no activity against <i>Pseudomonas aeruginosa</i> . Ceftolozane/tazobactam has activity against resistant G(-) pathogens (including <i>Pseudomonas aeruginosa</i>), <i>Enterobacteriaceae</i> , and some anaerobic pathogens (e.g., <i>Bacteroides fragilis</i>). Ceftobiprole is active against MRSA and <i>Streptococcus pneumoniae</i> resistant to third-generation CFs and penicillin, and G(-) bacteria associated with hospital-acquired pneumonia and community-acquired pneumonia.	

Physical-chemical properties. The chemical structure is based on the structure of ceftazidime (an oxyimino-aminothiazolyl CF), optimized to have activity on *Pseudomonas spp.* The aminothiadiazole moiety (attached to the side-chain from C7 position) confers increased activity against G(-) bacteria. Also, a pyrazole moiety attached to the side-chain from C3 position confers stability to beta-lactamases and permeability through the outer bacterial membrane. These properties of ceftolozane lead to increased activity against *Pseudomonas aeruginosa*. The parenteral formulation (1 g ceftolozane/0.5 g tazobactam powder for concentrate for solution for infusion) contains an equivalent amount of

ceftolozane sulphate and tazobactam sodium) [15].

Indications, dosing and administration. Usually, the approved dose of ceftolozane/tazobactam is 1 g ceftolozane/0.5 g tazobactam for the treatment of complicated intra-abdominal infections, urinary tract infections and acute pyelonephritis. Hospital-acquired pneumonia, including ventilator-associated pneumonia, require a dose of 2 g ceftolozane/1 g tazobactam. It is administered intravenously, every 8 hours (1 hour infusion time) for 4 – 14 days. It can be associated with metronidazole and other antibacterial agents for a broader antimicrobial spectrum [15,19].

Safety of ceftolozane/tazobactame. Generally, therapy with ceftolozane/tazobactam is well tolerated. The reported common side effects such as nausea, vomiting, diarrhea, constipation, abdominal pain, hypotension, rash, headache, dizziness, insomnia, anxiety, hypokalemia, thrombocytosis, and *Clostridioides difficile* colitis were mild or moderate [16,20]. Although contraindications for the use of ceftolozane/tazobactam have not been identified, precautions for use and special warnings are hypersensitivity reactions (may appear in patients allergic to beta-lactam antibiotics) and impairment of renal function [15]. In ceftolozane/tazobactam administration, no significant

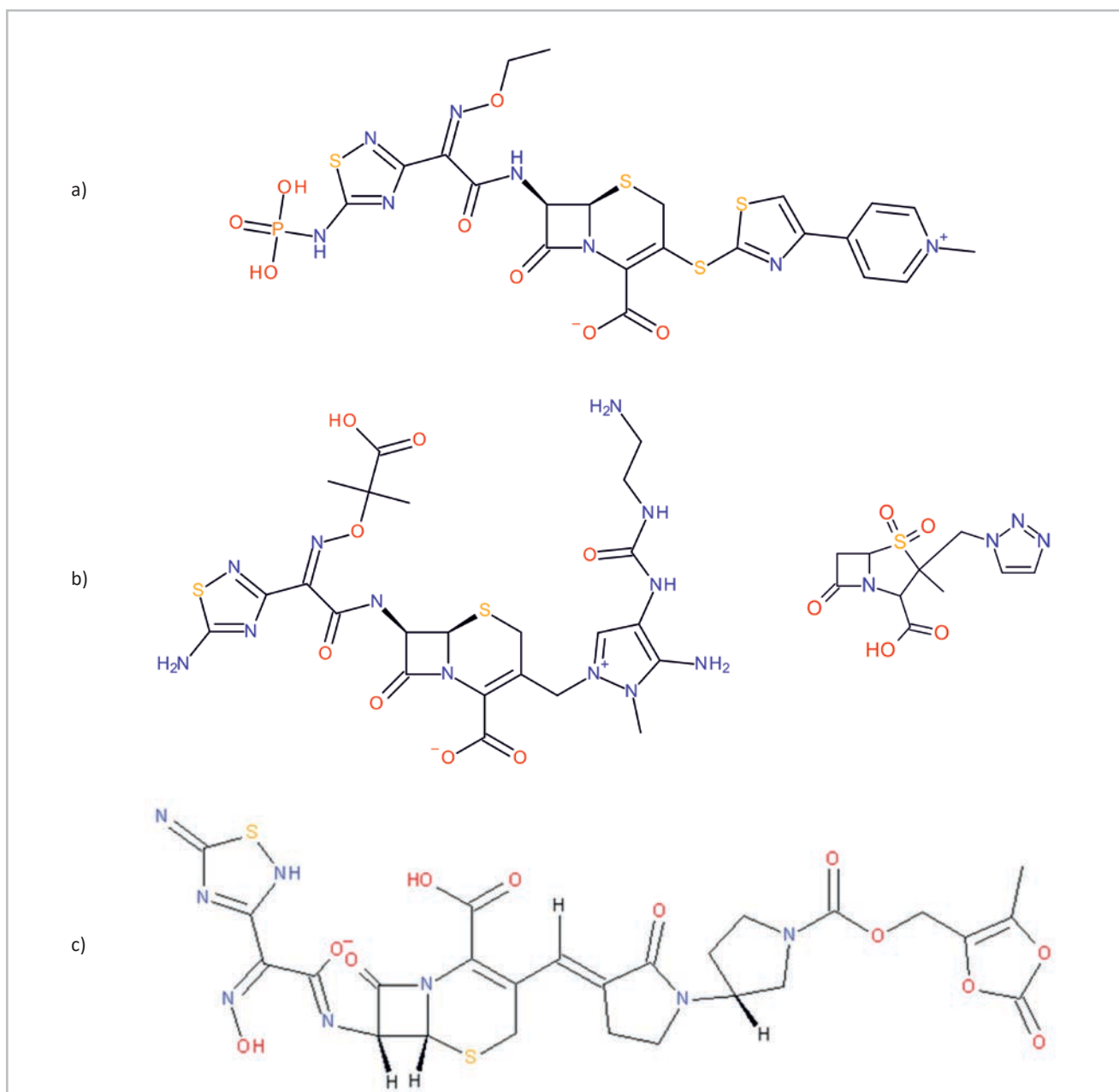


FIGURE 1. Chemical structures of a) ceftaroline fosamil; b) ceftolozane/tazobactam; c) ceftobiprole medocaril [18]

drug-drug or food-drug interactions have been reported. There is no data on ceftolozane/tazobactam effects in pregnancy, breastfeeding, or on fertility [15,20]. Unlike ceftaroline fosamil, ceftolozane/tazobactam combination is under evaluation for use in children [21].

Ceftobiprole medocaril

Ceftobiprole medocaril (ATC code: J01DI) is the prodrug form of ceftobiprole [22,23]. This fifth-generation cephalosporin has been

licensed in some European and non-European countries (Zeftera or Zevtera). However, ceftobiprole has not been approved by the FDA and EMA [22,24]. Ceftobiprole presents activity against MRSA, *Streptococcus pneumoniae* resistant to third-generation CFs and penicillin, and G(-) bacteria associated with hospital-acquired pneumonia and community-acquired pneumonia [3,22,25].

Physical-chemical properties.

Structurally, this new cephalosporin is an yrrolidinone-3-ylidenemethyl cephem [24]. The used pharmaceutical form is a water-soluble monosodium salt [23,24].

Indications, dosing and

administration. Ceftobiprole medocaril is indicated for the treatment of complicated skin and soft tissue infections and pneumonia [24]. Ceftobiprole medocaril is administrated

intravenously (500 mg every 8 hours over 2 hours in adults) during 4 - 14 days. Dosage adjustment is necessary for patients with moderate and severe renal impairment [23].

Safety of ceftobiprole medocaril.

Ceftobiprole has a good safety profile [3]. Nausea, headache and gastrointestinal disorders are the most common side effects of ceftobiprole [3,22]. Besides the broad spectrum of activity (including MRSA), the excellent safety profile of ceftobiprole medocaril is a significant advantage in comparison with other antimicrobial agents. However, there are no published studies regarding the usage of ceftobiprole medocaril in pregnancy, breastfeeding, effects on fertility, and drug-drug interactions [23]. The ongoing phase 3 studies will

contribute to the list of approved indications and will complete the knowledge on the use of ceftobiprole medocaril [3].

CONCLUSIONS

Ceftaroline fosamile, the combination ceftolozane/tazobactame, and ceftobiprole medocaril are the first representatives of the fifth-generation of CFs used in therapy. These new antibiotics are valuable anti-infective agents with a positive balance between benefits and side-effects. Nevertheless, the fifth-generation CFs should be highly restricted to prevent the occurrence of bacterial resistance. These new beta-lactam antibiotics must be judiciously used, only in the situation where other antibacterial drugs were not effective.

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