What is the role of ceftolozane-tazobactam (Zerbaxa™) in the hospital?

Introduction
Antibiotic resistance is a growing, world-wide problem. It is estimated that at least 2 million people in the United States acquire an antibiotic resistant infection on an annual basis.\(^1\) In fact, antibiotic resistant infections contribute to 23,000 deaths and cost up to $35 billion dollars annually – in the United States alone.\(^1\) In response to this challenge, the federal government, infectious diseases professional societies, and the pharmaceutical industry are pushing to develop new antibiotics that are effective against multidrug resistant organisms (MDROs).\(^2\)

One new promising agent, ceftolozane-tazobactam, will be the focus of this newsletter. Specifically, we will address the microbiology and pharmacology of ceftolozane-tazobactam. We will also discuss the wording and intent of the FDA’s approval of this agent and our opinion on when its use is a reasonable and appropriate option.

What is ceftolozane-tazobactam?
Ceftolozane-tazobactam, as the name suggests, is a combination of two separate compounds. Ceftolozane is a novel third-generation cephalosporin with \textit{in vitro} activity against a wide variety of Gram negative pathogens, including \textit{Pseudomonas aeruginosa}.\(^3\) However, ceftolozane, like other third-generation cephalosporins, is susceptible to inactivation (hydrolysis) by microorganisms that contain extended-spectrum beta-lactamase (ESBL) enzymes.\(^3\) Tazobactam, is a beta-lactamase inhibitor that prevents the inactivation of ceftolozane by ESBL enzymes. Thus, ceftolozane-tazobactam retains antimicrobial activity against many, but not all, ESBL-producing organisms.\(^3\)

Review of the microbiology and pharmacology of ceftolozane-tazobactam
Ceftolozane has two specific advantages over other older anti-pseudomonal drugs such as ceftazidime. First, ceftolozane has more affinity to drug binding sites on the surface of \textit{P. aeruginosa}.\(^4,5\) Second, ceftolozane has less affinity to binding to molecules such as AmpC beta-lactamases or other mechanisms, such drug efflux pumps, that \textit{P. aeruginosa} uses to produce resistance to cephalosporins.\(^6\)
The presence of tazobactam increases the efficacy of ceftolozane activity against ESBL-producing organisms and some anaerobic species.\(^7,8\)

Ceftolozane-tazobactam is less potent than cefepime and carbapenems against a few ceftazidime-resistant organisms such as *Enterobacter* and *Citrobacter* species. However, this reduced potency is curiously species dependent. For example, ceftolozane-tazobactam has excellent activity against *Pseudomonas aeruginosa* strains that are resistant to both ceftazidime and imipenem.\(^9\)

Ceftolozane-tazobactam’s utility as a single agent in the treatment of intra-abdominal infections has been inadequately studied. Thus, at present most experts are not comfortable using it without concurrent coverage against anaerobes. Ceftolozane-tazobactam had good *in vitro* activity against *Bacteroides fragilis, Fusobacterium spp.*, and *Propionibacterium spp.*, but its activity against Gram-positive cocci and other *Bacteroides spp.* is variable; it also has limited *in vitro* activity against *Clostridium spp.*\(^10\)

**Ceftolozane-tazobactam in clinical trials**

Ceftolozane-tazobactam has received approval by the Food and Drug Administration (FDA) for only two indications: complicated intra-abdominal infections and complicated urinary tract infections. The first indication was based on the results of a trial comparing ceftolozane-tazobactam 1.5g intravenously administered every 8 hours in combination with metronidazole that concluded the efficacy of this regimen non-inferior to meropenem.\(^11\) Common side effects of patients receiving ceftolozane-tazobactam in this trial included fever (15%), nausea (6%), anemia (6%), vomiting (5%), diarrhea (5%), and hypertension (5%). The FDA also gave approval for the use of ceftolozane-tazobactam in patients with complicated urinary tract infections based on a large phase 3 trial in which ceftolozane-tazobactam 1.5g intravenously administered every 8 hours was found to be non-inferior to levofloxacin 750 mg by mouth daily. The incidence of side effects in this study were low and similar to those in the levofloxacin group.\(^12\)

Clinical trials of high-dose ceftolozane-tazobactam are underway for the treatment of healthcare-associated pneumonia and ventilator associated pneumonia, but at present this drug is not approved for either of these indications.

**Summary and role in hospitals and clinics**

Ceftolozane-tazobactam appears to be a useful option for treating patients with complicated intra-abdominal infections and urinary tract infections in which multidrug resistant organisms are known or suspected to be pathogens. However, we do not believe it will replace more established therapies at this time.

Ceftolozane-tazobactam has several *in vitro* advantages over older antipseudomonal cephalosporins. These advantages include better activity against extended-spectrum beta-lactamase producing (ESBL) organisms and MDRO *Pseudomonas* isolates. However, further studies are required to determine if these *in vitro* advantages consistently translate into improved patient outcomes. Ceftolozane-tazobactam also has a better toxicity profile than other drugs used in difficult MDRO situations such as polymixin or colistin.
There are two big problems related to the widespread adoption of ceftolozane-tazobactam in most community hospitals. First, automated susceptibility testing or Kirby Bauer testing for ceftolozane-tazobactam is not widely available at this time. This lack of availability of susceptibility testing makes it unlikely that ceftolozane-tazobactam is an appropriate choice for treatment of patients known or suspected to have infections due to MDRO pathogens. Second, this drug is expensive. The current cost is approximately $249 dollars per day at Duke University Hospital. One online source estimates that a course of therapy may cost between $5,000 and $6,000 dollars per patient at most institutions.\(^{13}\)

In the future, we hope to see ceftolozane-tazobactam as a viable alternative to carbapenem therapy for the treatment of patients infected with ESBL-producing organisms and other MDROs. If this occurs, it is theoretically possible that reductions in carbapenem use will reduce the prevalence of carbapenem-resistant Enterobacteriaceae.

In the meantime, we recommend that physicians in community hospitals continue to preferentially use current antibiotics such as ciprofloxacin, levofloxacin, and piperillin-tazobactam that, in general, have comparable efficacy to ceftolozane-tazobactam. Ceftolozane-tazobactam may be beneficial in a small number of patients with known or suspected infections due to highly multidrug-resistant organisms, including certain multidrug-resistant strains of *Pseudomonas aeruginosa*. In these situations, we recommend consultation with microbiology staff and infectious disease specialists who can assist in navigating susceptibility testing needs and clinical complexity.

References


