A global crisis of antibiotic resistance is ongoing, especially with resistant gram-negative pathogens including *Pseudomonas* spp, carbapenemase-producing Enterobacteriaceae, and extended-spectrum β-lactamase (ESBL)-producing organisms. The increasing rate of methicillin-resistant *Staphylococcus aureus* (MRSA) infections is also a concern. One newer intravenous cephalosporin (ceftaroline) was approved in 2010, and 2 new intravenous cephalosporin–β-lactamase inhibitor combinations (ceftolozane-tazobactam and ceftazidime-avibactam) have recently been approved to try to combat these resistant organisms in adult patients.

Although it is certainly exciting to have additional antibiotic options to treat severe or resistant infections, unfortunately none of these agents offers a new mechanism of action or a new class of antibiotic. Rather, they extend the spectrum of coverage against resistant organisms relative to other antibiotics. Although individual pricing will vary by institution, these agents generally cost more than older comparable antibiotics, which will most likely affect formulary inclusion and criteria for use. Use of these new antibiotics is also likely to be restricted to antimicrobial stewardship programs and clinicians trained in infectious diseases. Susceptibility testing should be done whenever possible when these agents are used.

When using these newer antibiotics to treat severe, resistant infections off-label, especially when using higher doses or longer durations of therapy, clinicians must be vigilant about closely monitoring for toxic effects. This article discusses the pharmacology, limitations, and role of these antibiotics in treating infections in critically ill adult patients. The Table summarizes the indications, dosing, and renal dose adjustments for each antibiotic.

**Ceftaroline**

Ceftaroline (Teflaro) is a novel fifth-generation cephalosporin that was approved by the US Food and Drug Administration (FDA) in October 2010. This agent is unique relative to previously approved cephalosporins because it offers expanded coverage of gram-positive organisms, including MRSA, and also maintains activity against many common gram-negative organisms.

**Indications and Place in Therapy**

The FDA-approved indications for ceftaroline include acute bacterial skin and skin structure infections caused by susceptible strains of *S aureus* (including...
methicillin-susceptible \textit{S. aureus} (MSSA) and MRSA), \textit{Streptococcus pyogenes}, \textit{Streptococcus agalactiae}, \textit{Escherichia coli}, \textit{Klebsiella pneumoniae}, and \textit{Klebsiella oxytoca}. This agent is also approved to treat community-acquired bacterial pneumonia caused by susceptible isolates of \textit{Streptococcus pneumoniae} (including cases with concurrent bacteremia), \textit{S. aureus} (MSSA only because of the lack of adequate studies at this time to support MRSA pneumonia treatment), \textit{Haemophilus influenzae}, \textit{K pneumoniae}, \textit{K oxytoca}, and \textit{E. coli}.5

Beyond these FDA-approved uses, ceftaroline may be considered as an alternative therapy to treat serious MRSA infections or gram-negative pneumonia when more traditional agents are unable to be used because of clinical failure, resistance, or toxic effects. This agent may also be an option to consider for potential salvage therapy in patients with severe MRSA bacteremia, endocarditis, meningitis, osteomyelitis, or other serious infections.3,8-12

**Spectrum**

As mentioned earlier, ceftaroline has a relatively broad spectrum of activity, useful against staphylococci (MRSA and MSSA, including strains that are resistant to vancomycin), most streptococci, and common gram-negative bacteria, including \textit{E. coli}, \textit{H influenzae}, \textit{K pneumoniae}, and \textit{K oxytoca}. Of note, ceftaroline does not have reliable activity against \textit{Pseudomonas aeruginosa}, \textit{Stenotrophomonas maltophilia}, \textit{Proteus vulgaris}, \textit{Acinetobacter} spp, or ESBL-producing organisms. Ceftaroline also has minimal anaerobic activity and no activity against abdominal anaerobes like \textit{Bacteroides fragilis}.3

**Pharmacokinetics and Administration and Monitoring**

The prodrug, ceftaroline fosamil, is converted to active ceftaroline in the plasma.1 Ceftaroline has a half-life of approximately 3 hours, which is prolonged in patients with renal dysfunction. This agent is primarily eliminated renally and requires dose adjustment in patients with renal insufficiency and patients undergoing hemodialysis, with a need to adjust dosages starting at a creatinine clearance (CrCl) of 50 mL/min or less. Ceftaroline is administered by intermittent intravenous infusion in 5 to 60 minutes.

A typical regimen for ceftaroline to treat community-acquired pneumonia is 600 mg intravenously every 12 hours for 5 to 7 days. Complicated skin and skin structure infections are usually treated with ceftaroline 600 mg

### Table: Summary of Newer Intravenous Antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Indication</th>
<th>Dose</th>
<th>Renal Dose Adjustments</th>
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| Ceftaroline (Teflaro)               | ABSSI, CABP           | 600 mg every 12 h | CrCl >30 to ≤50 mL/min: 400 mg every 12 h  
|                                     |                       |                 | CrCl ≥15 to ≤30 mL/min: 300 mg every 12 h  
|                                     |                       |                 | CrCl <15 mL/min: 200 mg every 12 h  
|                                     |                       |                 | ESRD on IHD: 200 mg every 12 h  
|                                     |                       |                 | given after HD on dialysis days                                                   |
| Ceftolozane-tazobactam (Zerbaxa)6   | cIAI, cUTI            | 1.5 g every 8 h  | CrCl 30-50 mL/min: 750 mg every 8 h  
|                                     |                       |                 | CrCl 15-29 mL/min: 375 mg every 8 h  
|                                     |                       |                 | CrCl <15 mL/min not on dialysis: no dose adjustments provided  
|                                     |                       |                 | ESRD requiring IHD: 750 mg 1 time, then  
|                                     |                       |                 | 150 mg every 8 h, given after HD on dialysis days                                  |
| Ceftazidime-avibactam (Avycaz)7     | cIAI, cUTI            | 2.5 g every 8 h  | CrCl 31-50 mL/min: 1.25 g every 8 h  
|                                     |                       |                 | CrCl 16-30 mL/min: 0.94 g every 12 h  
|                                     |                       |                 | CrCl 6-15 mL/min: 0.94 g every 24 h  
|                                     |                       |                 | CrCl ≤5 mL/min: 0.94 g every 48 h  
|                                     |                       |                 | ESRD on IHD: Administer after HD on dialysis days; base dose on patient’s  
|                                     |                       |                 | estimated renal function                                                          |

Abbreviations: ABSSI, acute bacterial skin and skin structure infection; CABP, community-acquired bacterial pneumonia; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; CrCl, creatinine clearance; ESRD, end-stage renal disease; IHD, intermittent hemodialysis; HD, hemodialysis.
intravenously every 12 hours for 5 to 14 days. More aggressive regimens (eg, 600 mg intravenously every 8 hours) may be considered to treat more severe, refractory MRSA infections.9,13

Safety
Ceftaroline is a well-tolerated agent overall, with an adverse effect profile similar to that for other cephalosporins.1 Of note, in phase 3 trials, patients receiving ceftaroline demonstrated a positive result on an antiglobulin test (an indicator of autoimmune hemolytic anemia) more frequently than did patients in the comparison group. If patients receiving ceftaroline are exhibiting signs or symptoms of anemia, drug-induced hemolytic anemia should be considered as a possible cause and ceftaroline should be discontinued with supportive care provided.5,14

Ceftolozane-Tazobactam
Ceftolozane-tazobactam (Zerbaxa) is a novel, fifth-generation cephalosporin and β-lactamase inhibitor combination product that was approved by the FDA in December 2014. This product was the first time that a β-lactamase inhibitor had been combined with a cephalosporin. Neither ceftolozane nor tazobactam is available as a stand-alone product, and tazobactam has been marketed as a combination product with piperacillin under the brand name Zosyn for years.

Indications and Place in Therapy
Ceftolozane-tazobactam is approved by the FDA to treat complicated intra-abdominal infections, in combination with metronidazole, caused by Enterobacter cloacae, E coli, K oxytoca, K pneumoniae, Proteus mirabilis, P aeruginosa, B fragilis, S anginosus, Streptococcus constellatus, and Streptococcus salivarius. This agent is also approved to treat complicated urinary tract infections, including pyelonephritis, caused by E coli, K pneumoniae, P mirabilis, and P aeruginosa.4

Beyond these FDA-approved indications, ceftolozane-tazobactam may be considered as an alternative agent for directed therapy of multidrug-resistant, gram-negative organisms (eg, Pseudomonas) when more traditional agents cannot be used because of clinical failure, resistance, or toxic effects. This agent is an alternative to carbapenems and may be an attractive option to consider in place of colistin or aminoglycosides to use for salvage therapy owing to the toxic effects associated with these antibiotics, especially the nephrotoxic effects.

Spectrum
Ceftolozane-tazobactam has expanded gram-negative activity with the inclusion of tazobactam in this combination product. It has activity against gram-negative organisms including multidrug-resistant Pseudomonas spp and common ESBLs, but not carbapenemases. It also covers Streptococcus anginosus, Streptococcus constellatus, and Streptococcus salivarius, but does not have reliable activity against gram-positive bacteria such as enterococci and Staphylococcus spp. Although ceftolozane-tazobactam covers B fragilis, other anaerobic activity may be variable, and the addition of metronidazole is recommended to treat complicated intra-abdominal infections.

Pharmacokinetics, Administration, and Monitoring
The ceftolozane component of this product has a half-life of approximately 3 hours, whereas the tazobactam component has a half-life of approximately 1 hour. The combination drug is administered intermittently as a 60-minute intravenous infusion. Similar to other β-lactam antibiotics, ceftolozane-tazobactam is primarily eliminated unchanged in the urine and requires dose adjustments with CrCl of 50 mL/min or less, in patients with renal insufficiency and patients undergoing hemodialysis.

To avoid medication errors, it is important to note that ceftolozane-tazobactam is a combination product, and dosage recommendations are expressed as grams of the ceftolozane-tazobactam combination. To treat complicated intra-abdominal infections, the typical regimen of ceftolozane-tazobactam is 1.5 g intravenously every 8 hours for 4 to 14 days in combination with metronidazole. The usual regimen to treat complicated urinary tract infections, including pyelonephritis, is 1.5 g intravenously every 8 hours for 7 days.6 Serious infections may require 3 g intravenously every 8 hours; however, such dosing is not yet recommended in the prescribing information.15,16

Safety
Ceftolozane-tazobactam appears to be well-tolerated, and the adverse effect profile is comparable to that of other cephalosporins (eg, headache, fever, nausea, and diarrhea).4
Renal function must be monitored at least daily, especially in dynamic critically ill patients, as doses will need to be adjusted accordingly. In clinical trials, ceftolozane-tazobactam was less effective in patients with a CrCl of 30 to 50 mL/min. Ceftolozane-tazobactam is listed as pregnancy risk factor B.6

Ceftazidime-Avibactam
Ceftazidime-avibactam (Avycaz) is a new third-generation cephalosporin and novel β-lactamase inhibitor combination product that was approved by the FDA in February 2015. Ceftazidime has been a very well-known, widely used cephalosporin for decades, but, unfortunately, it is vulnerable to β-lactamases. Avibactam is a new β-lactamase inhibitor that has minimal antibacterial activity but works synergistically with ceftazidime to protect it and extend its activity. Avibactam is available only in this combination product.

Indications and Place in Therapy
The current FDA-approved indications for ceftazidime-avibactam include the treatment of complicated intra-abdominal infections, in combination with metronidazole, caused by E cloacae, E coli, K oxytoca, K pneumoniae, P mirabilis, Providencia stuartii, and P aeruginosa. Another FDA-approved indication is the treatment of urinary tract infections (including pyelonephritis) caused by Citrobacter freundii, Citrobacter koseri, Enterobacter aerogenes, E cloacae, E coli, K pneumoniae, Proteus spp, and P aeruginosa.7

Beyond these FDA-approved indications, and like ceftolozane-tazobactam, ceftazidime-avibactam is reserved for patients with limited treatment options.17 Thus, ceftazidime-avibactam may be considered as an alternative agent for targeted therapy of resistant gram-negative organisms when more traditional agents cannot be used because of clinical failure, resistance, or toxic effects. This agent also offers an alternative to carbapenems, aminoglycosides, and colistin for serious infections.

Spectrum
Ceftazidime-avibactam is active against most Enterobacteriaceae (including those that produce AmpC β-lactamase, some carbapenemases, and ESBLs) and P aeruginosa. Of note, ceftazidime-avibactam is not active against Acinetobacter spp and does not have reliable anaerobic and gram-positive activity.

Pharmacokinetics and Administration and Monitoring
The ceftazidime component of this product has a half-life of approximately 3 hours, whereas the avibactam component has a half-life of approximately 2.5 hours. Ceftazidime-avibactam is administered by intermittent infusion in 2 hours. Similar to ceftaroline and ceftolozane-tazobactam, ceftazidime-avibactam is primarily eliminated unchanged in the urine and requires dose adjustments at a CrCl of 50 mL/min or less in patients with renal insufficiency and patients undergoing hemodialysis.

Dosage recommendations for ceftazidime-avibactam are expressed as total grams of combination product. Typical dosing of ceftazidime-avibactam to treat a complicated intra-abdominal infection is 2.5 g intravenously every 8 hours, in combination with metronidazole, for 5 to 14 days. Usual dosing for treating complicated urinary tract infections (including pyelonephritis) is 2.5 g intravenously every 8 hours for 7 to 14 days.7

Safety
Reported adverse effects of ceftazidime-avibactam include abdominal pain, constipation, anxiety, and neurotoxic effects, including encephalopathy, coma, seizures, and myoclonus. Risk may be increased with renal insufficiency, so clinicians must ensure that doses are adequately adjusted for renal function. Of note, similar to ceftolozane-tazobactam, renal function must be monitored at least daily when using ceftazidime-avibactam and doses should be adjusted accordingly.17 In clinical trials, ceftazidime-avibactam was less effective in patients with CrCl of 30 to 50 mL/min, but this lower effectiveness may have been due in part to subtherapeutic dosing. Ceftazidime-avibactam is also listed as pregnancy risk factor B. In addition, a drug interaction is apparent between probenicid and ceftazidime-avibactam, and this combination should be avoided because of the potential for probenicid to increase serum concentrations of avibactam by decreasing its renal elimination.7,17

Conclusion
Resistant pathogens continue to cause severe infections in the intensive care unit, leading to increased morbidity and mortality. Several new parenteral antibiotics have been approved to assist clinicians in treating these challenging infections, including ceftaroline,
ceftolozane-tazobactam, and ceftazidime-avibactam. All of these agents, however, have limitations and the potential to result in resistance, and none offers a new mechanism of action. Thus, the need for investigational agents and vigilant antimicrobial stewardship is ongoing in an effort to preserve these and other agents for current and future generations.

REFERENCES

CE Test Instructions

This article has been designated for CE contact hour(s). The evaluation tests your knowledge of the following objectives:

1. Compare and contrast the spectrum of activity of newer intravenous (IV) antibiotics in the intensive care unit (ICU).
2. Discuss the role, including indications and place in therapy, of newer IV antibiotics in the ICU.
3. Summarize the safety implications associated with newer IV antibiotics in the ICU.

Contact hour: 1.0
Pharmacology contact hour: 1.0
Synergy CERP Category: A

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