The discovery of antibiotics heralded a new era of medicine; however, the curtain is beginning to draw on this golden age. Antimicrobial resistance has been increasing globally and has reached a point that the World Health Organization (WHO) identifies as a major threat to humanity. The WHO released a list of 12 bacteria that pose the greatest risk, and the three most critical are highly resistant gram-negative organisms: Pseudomonas aeruginosa, Acinetobacter baumannii, and Enterobacteriaceae species. In the United States, data from the Centers for Disease Control and Prevention suggest that more than 2 million infections each year are caused by resistant organisms and that antimicrobial resistance is blamed for 23,000 deaths annually.

Common mechanisms of antimicrobial resistance include the production of enzymes that degrade antibiotics (e.g., beta-lactamases); upregulation or reduction of membrane porins that reduce intracellular drug concentrations; or modifications to the target binding site. Beta-lactamase enzymes are categorized into four classes, A through D. Two concerning types of enzymes include extended-spectrum beta-lactamases (ESBL) and carbapenemases, which are responsible for the degradation of potent antibiotics such as piperacillin/tazobactam and ceftazidime, and the carbapenem class (ertapenem [Invanz, Merck], meropenem, doripenem [Doribax, Shionogi, Inc.], and imipenem/cilastatin). A summary of beta-lactamase enzymes is provided in Table 1. These highly resistant organisms can cause a variety of infections including complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), hospital- or ventilator-associated pneumonia (HAP/ VAP), or bloodstream infections. This further increases the complexity of treating patients due to the need for various pharmacokinetic or pharmacodynamic properties of the antibiotic to exceed the minimum inhibitory concentration (MIC) necessary to inhibit bacterial growth.

The growing threat of antimicrobial resistance has been coupled with a decline in the research and discovery of new and effective antibiotic agents. As a way to combat this, the Food and Drug Administration (FDA) has created the qualified infectious disease product designation to grant priority review and give the pharmaceutical industry incentives in this field. Over the past few years, newer antimicrobials have been brought to market (e.g., ceftazidime/avibactam [Avycaz, Allergan] and ceftolozane/tazobactam [Zerbaxa, Merck]), but there is still a vast clinical need for more potent, novel antimicrobials. This article will focus on new agents in development targeting highly resistant gram-negative organisms commonly found in the health care setting. A summary of the agents can be found in Table 2.

**Aztreoan/Avibactam**

Avibactam is a broad-spectrum beta-lactamase inhibitor with activity against class A, class C, and select class D beta-lactamase enzymes. A combination of avibactam with ceftazidime, a cephalosporin, was approved in 2015, but adoption of this combination has been slow due to concerns from limited reports of resistance. Pfizer is evaluating a new combination of avibactam with aztreonam, a monobactam antibiotic, for the treatment of multidrug-resistant (MDR) gram-negative infections. The clinical spectrum of aztreonam/avibactam demonstrated the strongest activity against Enterobacteriaceae organisms during *in vitro* evaluations and exhibited limited activity against *P. aeruginosa* and *A. baumannii*.

The REJUVENATE trial is an ongoing open-label, dose-confirming study evaluating the role of aztreonam/avibactam in the treatment of cIAIs. Outcomes data have yet to be reported. Pfizer is also planning another trial evaluating aztreonam/avibactam plus metronidazole versus meropenem plus colistin in the treatment of serious gram-negative infections (REVISIT), but this trial is not enrolling patients yet. Initial reports from phase 1 studies suggest aztreonam/avibactam is well tolerated, but data from larger trials will be needed to better assess this combination. Pending positive results from future trials, aztreonam/avibactam is anticipated to be approved in 2019. This combination possesses a

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**Table 1 Description of Beta-Lactamase Enzyme Classes**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class A</td>
<td>Hundreds of subtypes exist in this class&lt;br&gt;Examples: TEM, SHV, CTX-M, KPC&lt;br&gt;KPC subtypes can hydrolyze carbapenems; others can produce ESBL</td>
</tr>
<tr>
<td>Class B</td>
<td>Regarded as metallo-beta-lactamases due to the requirement of zinc for hydrolysis&lt;br&gt;Examples: IMP, VIM, SPM, NDM-1&lt;br&gt;Highly resistant to beta-lactamase inhibitors&lt;br&gt;Ability to hydrolyze carbapenems</td>
</tr>
<tr>
<td>Class C</td>
<td>Commonly seen in <em>Serratia, Pseudomonas, Acinetobacter, Citrobacter</em>, and <em>Enterobacter</em> organisms&lt;br&gt;Examples: AMP-C, ACT-1&lt;br&gt;Ability to produce ESBL</td>
</tr>
<tr>
<td>Class D</td>
<td>Variable activity against different classes of antibiotics&lt;br&gt;Example: OXA</td>
</tr>
</tbody>
</table>

ESBL = extended-spectrum beta-lactamase.
slight advantage in that it is safe for use in patients with a documented severe penicillin allergy; however, the lack of activity against *A. baumannii* and *P. aeruginosa* may limit its use in empiric treatment.

**Cefiderocol**

Cefiderocol is a cephalosporin being developed for the treatment of carbapenemase-producing gram-negative isolates. Despite its classification as a cephalosporin, the mechanism of cefiderocol differs from other agents in the class because it does not inhibit cell wall synthesis but rather chelates iron ions within the bacteria that are essential to the organism’s survival. This unique mechanism earned it the designation of a siderophore cephalosporin. In an *in vitro* evaluation against highly resistant gram-negative organisms, cefiderocol demonstrated high activity against carbapenem-resistant *Enterobacteriaceae*, MDR isolates of both *P. aeruginosa* and *A. baumannii*, *Stenotrophomonas maltophilia*, and *Burkholderia cepacia*.

Shionogi announced positive results from its phase 2 APEKS-cUTI trial in which cefiderocol demonstrated non-inferiority to imipenem/cilastatin in the treatment of 452 patients with cUTIs. Composite clinical and microbiological responses were 73% (183 of 252) for cefiderocol versus 55% (65 of 119) for imipenem/cilastatin; however, the clinical response rate alone was similar between the two groups at 90% versus 87%, respectively. Currently, two additional clinical studies are under way, evaluating the use of cefiderocol in the treatment of severe infections caused by carbapenem-resistant organisms (CREDIBLE-CR) and in gram-negative nosocomial pneumonia (APEKS-NP), with expected completion dates in 2018 and 2019, respectively. Cefiderocol has excellent potential to be a first-line agent when high levels of gram-negative resistance are suspected given its broad antimicrobial coverage and high activity against resistant organisms.

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### Table 2: Summary of Antimicrobial Agents in Clinical Development

<table>
<thead>
<tr>
<th>Drug Developer(s)</th>
<th>Mechanism of Action</th>
<th>Targeted Indication/Population</th>
<th>Route and Dose</th>
<th>Expected Price Strategy</th>
<th>Anticipated Launch Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aztreonam/avibactam Pfizer</td>
<td>Mono-bactam antibiotic plus beta-lactamase inhibitor</td>
<td>Serious gram-negative infections, including cIAI, cUTI, HAP/VAP, and patients with penicillin allergies</td>
<td>IV Dose ranges under study: 4,250–6,500 mg ATM/1,162–2,167 mg AVI on day 1, followed by daily dosing of 3,000–5,000 mg ATM/820–2,000 mg AVI</td>
<td>Similar in price to other fixed-dose patented regimens and significantly higher in price than aztreonam</td>
<td>Projected 2019</td>
</tr>
<tr>
<td>Shionogi and Co. Ltd.</td>
<td>Cephalosporin antibiotic</td>
<td>MDR gram-negative infections, including CRE, <em>P. aeruginosa</em>, and <em>A. baumannii</em></td>
<td>IV 2 g every 8 hours</td>
<td>Similar in price to other fixed-dose patented regimens and significantly higher in price than other cephalosporins or piperacillin/tazobactam</td>
<td>TBD</td>
</tr>
<tr>
<td>Pfizer</td>
<td></td>
<td>Hospital-acquired infections caused by MDR gram-negative bacteria, including cUTI and cIAI</td>
<td>IV 1–1.5 mg/kg every 12 hours</td>
<td>Similar in price to other patented fixed-dose medications and significantly higher in price than tigecycline</td>
<td>TBD</td>
</tr>
<tr>
<td>Tetraphase Pharmaceuticals</td>
<td>Tetracycline antibiotic</td>
<td>Treatment of cUTIs and possibly lower respiratory, skin, and soft-tissue infections</td>
<td>IV 800 mg once daily</td>
<td>Priced slightly above the cost of current fluoroquinolones</td>
<td>TBD</td>
</tr>
<tr>
<td>MerLion Pharmaceuticals</td>
<td>Fluoroquinolone antibiotic</td>
<td></td>
<td></td>
<td></td>
<td>TBD</td>
</tr>
<tr>
<td>Achaogen</td>
<td>Aminoglycoside antibiotic</td>
<td>MDR gram-negative bacteria, including ESBL and CRE organisms</td>
<td>IV 15 mg/kg once daily</td>
<td>Similar in price to other patented fixed-dose medications and priced higher than currently available aminoglycosides</td>
<td>2018</td>
</tr>
<tr>
<td>Merck</td>
<td>Beta-lactam antibiotic plus beta-lactamase inhibitor</td>
<td>Hospital-acquired infections caused by MDR gram-negative bacteria, including cUTI, cIAI, and pneumonia</td>
<td>IV 250 mg relebactam/500 mg imipenem/cilastatin every 6 hours</td>
<td>Similar in price to other patented fixed-dose medications and priced significantly higher than piperacillin/tazobactam</td>
<td>TBD</td>
</tr>
</tbody>
</table>

ATM = aztreonam; AVI = avibactam; cIAI = complicated intra-abdominal infection; CRE = carbapenem-resistant *Enterobacteriaceae*; cUTI = complicated urinary tract infection; ESBL = extended-spectrum beta-lactamase; HAP/VAP = hospital- or ventilator-associated pneumonia; IV = intravenous; MDR = multidrug resistant; TBD = to be determined.
Eravacycline
A highly anticipated upcoming agent is Tetraphase Pharmaceuticals’ eravacycline. This agent possesses potent activity against a number of MDR strains of both gram-positive and gram-negative bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant *Enterobacteriaceae* (CRE), and ESBL isolates. Current in vivo studies have demonstrated the high activity of eravacycline against *Enterobacteriaceae* species and *A. baumannii*, including organisms that are resistant to carbapenems, polymyxin, and cephalosporins; however, potent activity against *P. aeruginosa* was not seen. When compared to tigecycline, an older approved antibiotic of similar activity and structure, the MIC values of eravacycline tended to be twofold to fourfold lower.12

Two phase 3 clinical trials have been completed evaluating the use of eravacycline to treat cUTIs and cIAIs, and two additional studies are under way. The IGNITE-1 trial evaluated 541 patients receiving either eravacycline 1 mg/kg intravenously (IV) every 12 hours or 1 g ertapenem daily for four to 14 days for the treatment of cIAIs. This trial demonstrated eravacycline to be noninferior to ertapenem with clinical cure rates of 87% and 89%, respectively.13 The IGNITE-2 trial evaluated eravacycline 1.5 mg/kg IV once daily for either 100 mg or 250 mg orally every 12 hours compared with levofloxacin 750 mg daily given by IV or orally for the treatment of cUTIs in more than 900 patients. This trial failed to demonstrate that eravacycline was noninferior to levofloxacin for this indication, and it is speculated that this was due to the poor bioavailability of the oral formulation. Following these results, further developments of eravacycline are focusing on IV therapy. Throughout both trials, the most common adverse effects seen were gastrointestinal symptoms, such as nausea, vomiting, abdominal pain, or ileus. Tetraphase is planning additional follow-up studies to evaluate the use of eravacycline in the treatment of cUTIs (IGNITE-3) and cIAIs (IGNITE-4).4 The antimicrobial activity of eravacycline is very promising, but past experiences with tigecycline may limit initial clinician confidence until additional outcomes data are available. In addition, the ability to produce an oral formulation would have been a major advantage, making the failure of that trial a slight blow to development and the subsequent market.

Finafloxacin
Finafloxacin is a novel fluoroquinolone antibiotic being developed by MerLion Pharmaceuticals for the treatment of cUTIs with broad potential for other infections, such as cIAIs and pneumonia. Finafloxacin possesses a broad gram-positive and gram-negative spectrum of activity, which includes organisms such as *P. aeruginosa* and *A. baumannii*. One of the unique aspects of finafloxacin is its enhanced activity in an acidic environment, which may make it ideal for the treatment of abscesses or pulmonary infections.3

Despite initial positive trial results and fast-track designation from the FDA in 2013, the development process for finafloxacin has been slow. Limited clinical data have been released publicly, and MerLion has not indicated any intention to move forward with evaluation of finafloxacin in treating resistant gram-negative organisms. Only top-line results were released regarding the medication’s use in cUTIs, which showed higher efficacy compared with ciprofloxacin (89% versus 79%), but organism-specific data were not published except that 83% of isolates were *Escherichia coli*. In addition, limited safety data have been made available, making determinations on this parameter difficult.4

A potential reason for the lack of aggressiveness may be the perceptions key opinion-leaders hold regarding the medication. Clinicians view finafloxacin as a niche agent or are skeptical of the medication’s role in treating health-care–associated infections. MerLion has suggested that it may pursue finafloxacin in alternate roles, such as treatment of community-associated MRSA, chronic obstructive pulmonary disease exacerbations, or infections in cystic fibrosis patients. Currently, no clinical trials are under way.15

Meropenem/Vaborbactam
The combination of meropenem with the beta-lactamase inhibitor vaborbactam (Vabomere, The Medicines Company) received accelerated approval from the FDA in August 2017. It is approved for use in adult patients with cUTIs, including pyelonephritis, caused by designated susceptible *Enterobacteriaceae*.16,17 The company is still conducting trials to support use of the drug in pediatric patients with serious bacterial infections and in adults with bacterial HAP/VAP. These studies aim for completion by 2019 or 2020.18

The addition of vaborbactam allows meropenem to retain activity against select CRE organisms that produce certain beta-lactamase enzymes, but not against organisms with mechanisms of resistance that include efflux pumps, modified medication binding sites, or loss of porin channels. Vaborbactam demonstrates activity against beta-lactamases from the KPC, SME, TEM, SHV, CTX-M, CMY, and ACT families of enzymes but lacks activity against metallo-beta-lactamases.19

The efficacy of meropenem/vaborbactam was demonstrated in a single phase 3 trial evaluating 545 patients with cUTIs (TANGO I). Patients were randomized to receive either the combination of 2 g of meropenem plus 2 g of vaborbactam or piperacillin/tazobactam 4.5 g every eight hours and could be switched to oral therapy after receiving 15 IV doses. Ninety-eight percent of patients receiving meropenem/vaborbactam demonstrated clinical improvement and microbiological eradication at the end of IV therapy, which was similar to 94% of piperacillin/tazobactam patients. Subsequently, seven days after the completion of therapy, rates of symptom resolution combined with negative follow-up cultures were 77% and 73%, respectively. Adverse effects were mild and included headache, infusion-site reactions, diarrhea, nausea, and elevations in liver enzyme tests.19

A second trial, TANGO II, evaluated meropenem/vaborbactam compared with best-available therapy in a variety of infections, including cUTIs, cIAIs, bacteremia, or HAP/VAP with known or suspected CRE organisms. Forty-three patients had confirmed CRE and were evaluated with microbiological outcomes. Meropenem/vaborbactam appeared to perform better with lower all-cause mortality at day 28 (four of 16 patients [25%] versus four of nine patients [44%]). Given the small sample sizes, it is difficult to draw strong conclusions.20

Plazomicin
Achaogen is in the process of developing plazomicin, a next-generation aminoglycoside antibiotic, for use in resistant
gram-negative infections. Enzymatic modification is a common mechanism used to degrade other aminoglycosides, but plazomicin’s structure offers protection against bacterial interference, which preserves its activity. In October 2017, Achaogen submitted a new drug application to the FDA for the use of plazomicin to treat cUTIs and bloodstream infections, and the company stated it intends to submit for European Union approval in 2018.

Plazomicin was studied using a once-daily, 15-mg/kg IV dose in two clinical trials, EPIC and CARE. In the EPIC trial, clinicians compared plazomicin with meropenem in the treatment of cUTIs and acute pyelonephritis. The trial showed plazomicin was superior to meropenem when comparing microbial eradication in patients with a positive bacterial culture (87.4% versus 72.1%). Plazomicin demonstrated good activity against a variety of gram-negative organisms, including ESBL-producing, levofloxacin-nonsusceptible, and aminoglycoside-nonsusceptible Enterobacteriaceae. Plazomicin was generally well tolerated and had similar adverse effects compared with meropenem; however, a greater number of patients in the plazomicin group had a 0.5-mg/dL or greater rise in serum creatinine (7% versus 4%). The CARE trial compared the efficacy and safety of plazomicin with colistin, both in combination with other antibiotics, in the treatment of HAP/VAP, cUTIs, or bloodstream infections caused by CRE organisms. The primary outcome of all-cause mortality or significant disease-related complications at day 28 was lower in the plazomicin group compared with the plazomicin group (two of 14 patients [14%] versus eight of 15 patients [53%], respectively), though strong conclusions are difficult to draw given the small number of patients.

While initial data with plazomicin appear promising, broad use of this medication may be limited by clinicians’ underlying hesitancy to use aminoglycosides given the adverse effects of nephrotoxicity or ototoxicity associated with older agents in this class. In addition, there are few clinical data available regarding the use of plazomicin against isolates of P. aeruginosa and A. baumannii, which may limit the uptake of this agent into clinical practice.

Imipenem/Cilastatin/Relebactam

Relebactam is a next-generation beta-lactamase inhibitor with activity against ESBL and CRE enzymes, with the exception of Class B metallo-beta-lactamases. Merck is exploring the combination of imipenem/cilastatin with relebactam for the treatment of complicated gram-negative infections. Relebactam enhances the activity of imipenem against resistant isolates of Klebsiella pneumoniae and P. aeruginosa, but not A. baumannii. When evaluating a variety of resistant gram-negative isolates with reduced imipenem/cilastatin susceptibility, the addition of relebactam lowered the MIC values a median of 32-fold (range, 0.5–256).

Data from phase 2 trials have shown relebactam/imipenem to be noninferior to imipenem/cilastatin alone in the treatment of cIAIs and cUTIs. Patients with cUTIs or pyelonephritis receiving imipenem plus either 125 mg or 250 mg of relebactam were found to have similar clinical (97% to 98%) and microbiological (95% to 98%) responses to those receiving imipenem/cilastatin monotherapy. Imipenem/relebactam also cleared all imipenem-nonsusceptible isolates. When evaluating 351 cIAI patients, imipenem/relebactam also demonstrated noninferiority to imipenem/cilastatin monotherapy, with clinical cures in the range of 95% to 99%. In both trials, imipenem/relebactam was well tolerated with adverse effects similar to imipenem monotherapy. A limitation of these initial trials was the low number of imipenem-resistant organisms evaluated, which made it difficult to extrapolate imipenem/relebactam’s real-world application.

Two phase 3 trials are under way to better examine the efficacy and safety of imipenem/relebactam. The RESTORE-IMI 1 trial comparing imipenem/relebactam with imipenem and colistin was completed in September 2017 and enrolled 50 patients with cIAIs, cUTIs, or HAP/VAP; however, results have not yet been released. A second, larger trial, RESTORE-IMI 2, is evaluating imipenem/relebactam versus pipercillin/tazobactam and is aiming to enroll 536 patients with HAP/VAP, with expected completion by 2019.

CONCLUSION

While the potential of upcoming anti-bacterial agents appears promising, it is difficult to predict long-term durability of the medications once they are widely used in clinical settings. The role of each individual agent will become clearer once each medication’s pharmacokinetics and pharmacodynamics are better characterized in a variety of patient populations and disease states. Once clinicians are familiar with these agents, the novel activity against highly resistant organisms may help to usher in a new golden age of antibiotics.

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