TRENDS-in-MEDICINE

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SUMMARY

Treatment of multidrug-resistant pathogens, particularly gram-negative bacilli, is a growing global problem. Complex mechanisms of resistance make treatment of these organisms challenging, with gram-negative carbapenem-resistant pathogens among the most serious threats. Recent new drug approvals and advancement of compounds to address this urgent threat include drug combinations that contain beta-lactamase inhibitors.

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IDWeek 2016:
Update on the Current Landscape of Treatment for Gram-Negative Infections
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At IDWeek 2016, several symposia and oral/poster abstract sessions focused on trends in gram-negative resistance and strategies to circumvent gram-negative resistant pathogens. The research found that the rising prevalence of infections due to multidrug-resistant (MDR) gram-negative bacteria presents a dilemma in selecting empiric antimicrobial therapy in seriously ill patients, making knowledge of the properties of available agents and the susceptibilities of the pathogens paramount. Rapid molecular diagnostics (RMD) and use of pharmacokinetic/pharmacodynamic (PK/PD) principles appear to have a positive impact in managing MDR organisms.

The Problem

Resistance in gram-negative bacilli continues to be a growing global problem. According to the President's Council of Advisors on Science and Technology, the threat of MDR bacterial strains on public health has risen to the level of a crisis. The United Nations also recognized the threat posed by MDR strains, with the Director General calling anti-microbial resistance a fundamental threat to global health and safety.

Infections due to MDR pathogens represent a significant burden on the healthcare system with increased morbidity and mortality, prolonged length of stay, and high hospital costs. The emergence of MDR pathogens limits treatment options at a time when the number of new antimicrobials has diminished.

Whether the organism is *Escherichia coli (E. coli)*, *Klebsiella pneumoniae (K. pneumoniae)*, *Acinetobacter baumannii (A. baumannii)*, or *Pseudomonas aeruginosa (P. aeruginosa)*, the rate of resistance to third-generation cephalosporins (e.g., ceftriaxone and ceftazidime) is rising. Among the most serious threats are gram-negative carbapenem-resistant pathogens. Resistance mechanisms include loss of porins, upregulation of efflux pumps, alteration of targets to prevent binding to the active site, and expression of beta-lactamases.

MDR pathogens threaten the ability to treat patients adequately. Basic principles of managing gram-negative MDR pathogens include:

- Knowledge of the local antibiogram, so that appropriate antibiotics can be started quickly.

- Prompt appropriate antimicrobial initiation (within 50 minutes), which has been shown to improve the odds of survival.
- Using rapid susceptibility testing to inform therapy and allow rapid de-escalation, reducing selection pressure for resistance.
- Optimizing dosing strategies, such as administering prolonged infusion with beta-lactams, which can maximize the time above the minimum inhibitory concentration (MIC) and potentially reduce the length of hospital stay and mortality.

Antimicrobial stewardship represents a possible solution. The Centers for Disease Control and Prevention (CDC) estimates that if best infection control practices and antibiotic stewardship were adopted nationally, >600,000 infections and 37,000 deaths could be prevented over 5 years.

SURVEILLANCE OF GRAM-NEGATIVE INFECTIONS

Becton Dickinson database

Hospital-onset MDR *P. aeruginosa* is known to be significantly more common than in the admission setting in U.S. hospitals, with 1 in 6 *P. aeruginosa* isolates thought to be resistant to multiple drugs. An electronic research database, maintained by Becton Dickinson, with records from 348 U.S. hospitals, was examined by researchers to identify national and geographic trends in gram-negative infection prevalence and susceptibility. The review found:

- An MDR *P. aeruginosa* rate of 17.2% for the hospital-onset setting versus 12.3% in the admission setting, with significant regional differences. Thus, hospitals in different geographic regions need to be aware of their local microbiologic epidemiology for MDR *P. aeruginosa* when selecting empiric antibiotic therapy for patients at risk of infection with *P. aeruginosa*.
- *P. aeruginosa* isolates from respiratory, blood, wound, and urine had non-susceptibility rates of 32.8% for ciprofloxacin/levofloxacin, 19.8% for ceftazidime, 19.5% for Bristol-Myers Squibb's Maxipime (cefepime), 20.5% for Pfizer's Merrem (meropenem, formerly an AstraZeneca drug), and 13.7% for Pfizer's Zosyn (piperacillin-tazobactam). Respiratory had the highest rate of non-susceptibility for all of the antibiotics.
- Regional differences in the susceptibility of extended-spectrum beta-lactamases (ESBLs) producing *E. coli*, *K. pneumoniae*, and *Proteus mirabilis* (*P. mirabilis*) isolates in different healthcare settings (admission, hospital-onset, and ambulatory), with an overall ESBL rate of 6.9%. The highest rate was in the hospital-onset setting (13.3%). The highest ESBL region had a rate approximately twice that of the lowest region in all three settings.
- Hospital-onset carbapenem-resistant *Enterobacteriaceae* (CRE) events over a 1-year period (July 2015-June 2016) were more common than previously reported. *E. coli*, *K. pneumoniae*, and *P. mirabilis* isolates identified and tested for susceptibility in >700,000 patients found that 0.7% were CRE, with the percentage highest in the hospital-onset period (1.9%), followed by admission (1.0%) and ambulatory (0.5%) settings. The national projected number of carbapenem-resistant *E. coli*, *K. pneumoniae*, and *P. mirabilis* events was >53,000. The number of projected cases was highest in the Midwest and South.

Intermountain Healthcare

Rates of methicillin-resistant *Staphylococcus aureus* (MRSA) have been declining, but it remains the most common antibiotic-resistant bacteria, and the incidence is higher among the larger hospitals of Intermountain Healthcare System's 22 hospital system. Other trends from examination of Intermountain's electronic dataset:

- 70% of MDR organisms over the past 8 years originated from the ambulatory setting.
- 70% of MDR organisms detected in admitted patients were attributed to acquisition in non-acute care settings.
- The rate of *Clostridium difficile* infection is increasing with more sensitive tests to detect it.
- The rate of ESBL infections continues to increase faster than other antibiotic-resistant bacteria.

Premier

In an examination of the Premier hospital database from 2010-2015, *A. baumannii* and *P. aeruginosa* were found to account for a far greater number of carbapenem-resistant infections than *K. pneumoniae* and *E. coli*, a trend that was consistent over time. From 38.1%-54.3% of patients infected with *A. baumannii* and 19.4%-22.7% infected with *P. aeruginosa* were carbapenem-resistant vs. only 3.6%-5.6% of *K. pneumoniae* and 0.3%-0.4% of *E. coli*. Crude in-hospital mortality rates ranged by carbapenem-resistant pathogens from 10.5% for *E. coli* to 15.7% for *A. baumannii*.

In another evaluation of 10,634 U.S. hospitalized patients in the Premier hospital database between January 2011 and December 2014 with invasive hospital-onset infections due to *Enterobacteriaceae*, the overall presence of CRE was 4.5%

(481 of 10,634). *Enterobacteriaceae* was considered carbapenem-resistant if it was non-susceptible to meropenem, imipenem, doripenem, or ertapenem. Factors associated with an increased risk of CRE included a >2% prevalence of CRE in the hospital where the patient was admitted, receipt of dialysis in the current hospital admission, evidence of an infection in the 3 months prior to the current hospitalization, and the cumulative number of antibiotic exposures in the current or a previous hospital admission.

Earlier identification methods for infection with gram-negative resistant pathogens may shorten time to appropriate therapy, potentially improving outcomes. Investigators examined outcomes for 6,055 patients in the Premier database with evidence of serious infection, 46% who received delayed appropriate therapy and 54% who had appropriate therapy initiated within ≤2 days of index culture. Compared with delayed administration, timely administration resulted in 3.7 fewer days of therapy ($p<0.01$) and a 4.1-day shorter length of hospital stay ($p<0.01$). Total cost of therapy was ~$18,000 for patients receiving timely administration vs. ~$25,000 for those with delayed therapy ($p<0.01$).

Rapid molecular diagnostics (RMD)

RMDs can be used to inform empiric therapy against beta-lactam-resistant *P. aeruginosa*. In a study, three RMD platforms were used to identify genes potentially conferring resistance or susceptibility to Merck's Zerbaxa (ceftolozane-tazobactam) and Allergan's Avycaz (ceftazidime-avibactam). Twenty-seven percent of 200 archived *P. aeruginosa* isolates were resistant to ceftolozane-tazobactam, and 23% were resistant to ceftazidime-avibactam by MICs. Susceptibility predictive values were ≥97% across all 3 platforms. The resistance predictive values (RPVs) of molecular beacons were 62% for ceftolozane-tazobactam and 48% for ceftazidime-avibactam. The estimated RPVs of nanosphere and polymerase chain reaction coupled to electrospray ionization mass spectrometry were similar: 72% for ceftolozane-tazobactam and 60% for ceftazidime-avibactam.

UPMC

Carbapenem-resistant organisms have emerged in "waves" over time at the University of Pittsburgh Medical Center (UPMC), and antibiotic consumption does not appear to be associated with the epidemiology. These organisms are associated with high rates of mortality: 19.5% at 30 days and 31.9% at 90 days. Predictors of higher mortality were *A. baumannii* infection, age >65 years, and residence in the intensive care unit. Being a solid-organ transplant recipient predicted lower overall mortality. The overall mortality associated with *P. aeruginosa* has been decreasing since 2007.

VA

A first epidemic of carbapenem-non-susceptible/resistant *K. pneumoniae* in Veterans Administration facilities originated in the Northeast. A second epidemic of carbapenem-non-susceptible/resistant *Enterobacter cloacae* was centered in VA facilities in the West.

Toronto

A web-based mobile platform was developed at the University of Toronto and Boston Children's Hospital to aggregate and disseminate regional patterns in antimicrobial resistance indices. It generates estimates of resistance comparable to traditional surveillance estimates. The platform was found to have 94%-97% agreement to U.S. and Canadian indices for 2013 and 2014, and 92% agreement with state-specific resistance estimates.

THE KEY DRUGS FOR TREATING RESISTANT INFECTIONS

Michael Dudley, PharmD, senior vice president/head of research and development, infectious diseases global innovation group, for The Medicines Company, provided an update of recently approved agents and those in late clinical phase development for the treatment of gram-negative pathogens. He noted encouraging progress in approvals and advancement of compounds that address urgent and serious antimicrobial resistance threats, including combinations that contain beta-lactamase inhibitors. While these agents have variable activity against *Pseudomonas* spp. and *Acinetobacter* spp., clinical trials have focused on uses and indications in which *Enterobacteriaceae* are most prevalent. He said:

- In beta-lactam combination agents, the choice of the partner beta-lactam is important, with the activity and stability of the partner beta-lactam to older enzymes, such as ESBL-producing organisms, desirable.
- Reports of resistance developing to the partner should be considered in the use of beta-lactam combinations.
- There has been an emergence of ceftazidime-avibactam resistance due to bla_{KPC-3} mutations.
- The pharmacologic properties of the combination agents should match closely.

Clinical trials in the treatment of carbapenem-resistant gram-negative infections are ongoing with several agents, including Merck's 3-drug combination of imipenem-cilastatin-relebactam (MK-7655A). Following is a review of data from a number of studies presented at IDWeek.

ACHAOGEN's plazomicin

This is a novel aminoglycoside in Phase III development for the treatment of serious *Enterobacteriaceae* infections, including CRE. It was designed to be unaffected by the most common aminoglycoside-modifying enzymes that are responsible for gentamicin-, tobramycin-, and amikacin-resistance. Plazomicin has good activity against CRE but not in methylase-producing strains. Significant PK variability suggests that individualized plazomicin dosing will be needed to ensure target exposures are achieved. Risks of nephrotoxicity and tinnitus will also require therapeutic drug monitoring.

ALLERGAN's Avycaz (ceftazidime-avibactam)

Resistance to ceftazidime due to ESBLs and *K. pneumoniae* carbapenemase (KPC)-producing organisms has been observed, whereas ceftazidime activity is potentiated and restored when combined with avibactam. The activity of this combination against *P. aeruginosa* is variable and is dependent on low efflux. Ceftazidime-avibactam was approved by the FDA for the treatment of complicated urinary tract infections (cUTIs) based on Phase II data. A Phase III study in this indication has been completed and is under FDA review.

Avycaz was approved by the FDA for the treatment of complicated intra-abdominal infections (cIAIs) based on a Phase III trial in which it was found to be non-inferior to Merrem (meropenem), but efficacy of ceftazidime-avibactam was decreased in patients with creatinine clearance of 30-50 mL/min, after which the recommended dosage in patients with renal impairment was revised.

Avycaz was shown to be comparable to best available therapy, mostly carbapenems, in the treatment of ESBL infections. Prolonged infusion (over 2 hours) given every 8 hours optimizes the PK/PD properties of the drug.

■ The experience at Cleveland Clinic with 81 courses of ceftazidime-avibactam administered between April 2015 and February 2016 found that the rate of clinical cure for infections caused by KPC-producing CRE for off-label indications was 77.6%. Clinical cure was achieved as monotherapy in 18 of 20 patients (90%) and as part of combination therapy in 20 of 29 patients (69%). A pooled analysis of five Phase III clinical studies that included >2,000 patients demonstrated the efficacy of ceftazidime-avibactam in the treatment of cIAI and cUTI caused by MDR pathogens. Per-pathogen microbiologic response rates for MDR pathogens in the *Enterobacteriaceae* group were 76.7% for ceftazidime-avibactam vs. 69.0% in comparator arms. The microbiologic response rates for MDR *P. aeruginosa* were 71% and 78.9%, respectively.

■ A retrospective chart review of 10 patients with carbapenem-resistant *Pseudomonas* infections (any body site) treated with ceftazidime-avibactam at 3 U.S. hospitals found clinical success in 7 and microbiologic cure in 5. In-hospital mortality occurred in 2 patients. The researchers concluded that ceftazidime-avibactam can be considered for patients with MDR organisms causing *Pseudomonas* infections.

■ A retrospective case series from 9 U.S. hospitals that included 60 adults who received ceftazidime-avibactam for CRE infection showed clinical success in 65% and microbiologic cure in 53%. More than half of the patients were in the ICU at the time of ceftazidime-avibactam treatment. In-hospital mortality occurred in 32%, demonstrating the critical nature of these infections. *K. pneumoniae* was the causative pathogen in 80% of the cases.

■ Ceftazidime-avibactam has proven to be an effective treatment for CRE infections, but resistance can emerge rapidly during the treatment of carbapenem-resistant *K. pneumoniae* infections, UPMC researchers reported. In their review of patients treated with ceftazidime-avibactam for carbapenem-resistant *K. pneumoniae* at UPMC, resistance occurred in ~10% and was conferred by mutations in bla_{KPC-3}.

Of 51 patients treated with this combination at UPMC for CRE infections between April 2015 and September 2016, 42 were treated for carbapenem-resistant *K. pneumoniae*. Resistance emerged in 4 patients following 10-19 days of treatment and was associated with a ≥4-fold increase in ceftazidime-avibactam minimum inhibitory concentrations. Resistance was conferred by mutations in bla_{KPC-3} Ω-loop and adjacent sites.

The key mutation appears to be D179Y at the C-terminal end of the Ω-loop. Ryan Shields, PharmD, a researcher in the Division of Infectious Diseases at UPMC, said that the presence of the mutations on highly mobile genetic elements is concerning and suggests dissemination of resistance if ceftazidime-avibactam is used widely. At UPMC, ceftazidime-avibactam is positioned as a front-line agent for the treatment of CRE infection since it was approved by the FDA in 2015, but he said, "It is not a magic bullet."

Effective stewardship strategies and judicious use of ceftazidime-avibactam is needed, particularly the use of PK/PD-based dosing regimens to try to preserve this agent for the longest period possible. Arjun Srinivasan, MD, CAPT, associate director for healthcare associated infection prevention programs in the Division of Healthcare Quality Promotion at the CDC, said, "This is certainly a definite warning…We must be very careful about how we use this drug because resistance can develop, and it looks like it can develop pretty fast."

THE MEDICINES COMPANY's Carbavance (meropenem-vaborbactam)

Dr. Dudley said the potency of a carbapenem against *E. coli* and *Klebsiella* spp. can be recognized in this combination. He said vaborbactam appears to restore meropenem activity against *Enterobacteriaceae* spp., particularly those that are carbapenem-resistant, with 50%-70% of isolates being inhibited by <0.06 µg/mL of meropenem in the presence of vaborbactam. The PK properties of meropenem-vaborbactam are well-matched in plasma and epithelial lining fluid. The MICs against *Pseudomonas* spp. and *Acinetobacter* spp. are the same as with meropenem, with the 2 g dose of meropenem over 3 hours covering MICs of 4-8 µg/mL.

A double-dummy, 550-patient, 10-day Phase III trial in cUTI, including acute pyelonephritis, randomized patients to meropenem-vaborbactam vs. Pfizer's Zosyn (piperacillin-tazobactam). To be eligible for the study, patients had to have had at least 5 days of study IV antibiotics. Overall success at the end of the IV therapy was 98.4% for Carbavance patients vs. 94.0% for Zosyn patients, which met the criteria for superiority for Carbavance. Overall success at the test of cure visit (1 week after finishing treatment) was 74.5% for Carbavance vs. 70.3% for Zosyn. The rate of microbial eradication also favored Carbavance, meeting the non-inferiority endpoint.

MERCK's Zerbaxa (ceftolozane-tazobactam)

Dr. Dudley said ceftolozane's activity against *P. aeruginosa* is an advantage in this combination. The MIC creeps up in the case of carbapenem-resistant *P. aeruginosa*, so many carbapenem-resistant strains will be resistant to ceftolozane-tazobactam. Because tazobactam is a poor inhibitor of KPC-producing strains of *Enterobacteriaceae*, this combination agent does not have activity against MDR or KPC-producing *Klebsiella* spp. or *Enterobacteriaceae* spp. Ceftolozane-tazobactam is active against ESBL-producing organisms, but the level of potency is inferior to that of a carbapenem antibiotic. Phase III clinical trials support this combination's use in cUTIs and cIAIs.

A case series of 35 patients from 5 large U.S. academic centers showed that ceftolozane-tazobactam, which is approved for the treatment of cUTI and cIAI, appears to be a useful alternative for the treatment of carbapenem-resistant *P. aeruginosa* infections, but susceptibility testing is probably warranted because resistance was observed. This review of patients treated for ≥72 hours with ceftolozane-tazobactam for carbapenem-resistant *P. aeruginosa* found that clinical success was achieved in 74% of patients, but therapy failed in all 4 patients with ceftolozane-tazobactam non-susceptible *P. aeruginosa*.

PFIZER's Zosyn (piperacillin-tazobactam)

The 14-day mortality in patients hospitalized with monomicrobial ESBL bacteremia at Albert Einstein Medical Center was 11% in a group of 44 patients treated empirically with carbapenems vs. 43% in the 35 patients treated empirically with piperacillin-tazobactam. The results suggest that carbapenems be used as preferred empiric therapy for patients at high risk of ESBL bloodstream infections, although the authors admitted there is a possibility of resistance emerging with liberal use.

TETRAPHASE PHARMACEUTICALS' eravacycline (TP-434)

This fluorocycline is similar to glycylcyclines, but is 2-4 times as potent as Pfizer's Tygacil (tigecycline). In Phase III trials, IV/oral eravacycline was shown to be non-inferior to Merck's Invanz (ertapenem) for the treatment of cIAI but failed to meet the non-inferiority endpoint vs. IV/oral levofloxacin for the treatment of cUTI. Because the switch to oral eravacycline in this trial failed, a new formulation is being designed.

THE BOTTOM LINE: FOR MDR ORGANISMS, CONSULT EARLY WITH AN ID SPECIALIST

In a single-center study, consulting an infectious diseases clinician on MDR gram-negative urinary tract infections (or bacteremias) reduced in-hospital mortality and decreased the time to defervescence (abatement of fever). Among 205 patients enrolled, 65 received an ID consult (40 early consults and 25 late consults). In-hospital mortality was 29% among the patients with an early consult, 60% among those who received a late consult, and 30% among those not receiving a consult at all. Time to defervescence was 1.8 days for the early-consult group, 5.3 days for the late-consult group, and 4.9 days for those not receiving a consult.

■