The emergence of carbapenem-resistant Enterobacteriaceae (CRE) must be considered one of the most frightening consequences of microbial evolution in the last 2 decades. CRE is one of the top unmet medical needs for new antimicrobial approaches [1, 2]. These pathogens are extremely drug resistant, meaning that they resistant to all available antibiotics except those known to be inferior in efficacy or safety [3]. Patients with infections caused by CRE suffer from high mortality rates that are triple to quadruple the rates of infections caused by carbapenem-susceptible bacterial strains [4–6]. In patients with bacteremia caused by CRE and treated with initially ineffective therapy, mortality has exceeded 60% [7]; these are “pre-antibiotic era” equivalent numbers. The clarion call for new ways to treat such infections has been sounding for years [8–10].

A great relief for the infectious diseases (ID) community occurred when the first new combination drug that could treat CRE became available in 2015 [11]. Hope emerged. The novel β-lactamase inhibitor, avibactam—a bridged diazabicyclo[3.2.1]octanone non-β-lactam inhibitor—protects its partner antibiotic, ceftazidime, from hydrolysis by most serine cephalosporinases and carbapenemases. A key enzyme targeted is the Klebsiella pneumoniae carbapenemase (KPC) [12], which predominates in the United States and Europe. Regrettably, avibactam does not demonstrate inhibitory activity against metallo-β-lactamases, such as the New Delhi metallo-β-lactamases, Verona integrin-encoded metallo-β-lactamases, or IMP (active on imipenem), which predominate in much of the rest of the world. Thus, although we rejoiced, the ID community knew from the earliest moment of its availability that ceftazidime-avibactam was only a partial solution to our CRE problem.

Another concern, was ceftazidime the best “partner” antibiotic for avibactam [11]? Numerous observations in clinical and scientific literature suggested that ceftazidime was the cephalosporin most closely linked to the emergence of extended-spectrum β-lactamases (ESBLs) [13, 14]. Thus, concern regarding the potential for emergence to resistance has been long standing. So, how long will efficacy of ceftazidime-avibactam last, and how effective is it in treating CRE infections?

We have clinical trial data evaluating ceftazidime-avibactam for the treatment of both complicated urinary tract infections (cUTIs) and complicated intraabdominal infections (cIAIs) [15, 16]. The drug was found to be noninferior to comparator antibiotics for these infections (with a caveat that outcomes with ceftazidime-avibactam were markedly inferior in patients with cIAIs who had creatinine clearances <50 mL/min). However, patients enrolled in these trials were not infected with highly resistant pathogens such as CRE. Thus, while these trials demonstrated efficacy of the drug, and we know the drug has in vitro activity against KPC-producing strains of CRE, we have no published studies describing outcomes of patients infected by CRE and treated with ceftazidime-avibactam.

The good news is that Shields et al have provided us with a retrospective case series describing just such experience. The bad news is that the experience was alarming and unsettling [17]. During a 10-month period at the University of Pittsburgh Medical Center, they identified 37 patients infected with CRE and treated with ceftazidime-avibactam. Almost one third of patients were status post solid organ or hematopoietic transplant. Surprisingly, median Charlson comorbidity scores were in the bottom half of the score range, and median severity of illness scores (simplified acute physiology score [SAPS] II, sequential organ failure assessment [SOFA]) were in the bottom third, indicative of a moderately ill rather than a critically ill population of patients.

A mixture of infections was seen, with pneumonia (n = 12) and bacteremia (n = 10) most common; kidney, abdominal, skin and soft tissue, and mediastinal infections were also encountered. The predominant infecting species was Klebsiella pneumoniae; however, Escherichia coli and Enterobacter cloacae were also encountered. All initially recovered CRE.
isolates were considered susceptible to ceftazidime-avibactam, with a median (range) minimum inhibitory concentration (MIC) of 1 (0.25–4) µg/mL. KPC was the most common β-lactamase encountered (n = 29), with the remainder comprised of cephalaxine-munich, oxacillinase, sulfhydryl variable, and AmpC ESBLs. Metallo-β-lactamases were not encountered.

Ceftazidime-avibactam was predominantly used as monotherapy; however, approximately 30% of patients received combination regimens, primarily with aminoglycosides as the second agent. Treatment lasted for a median of 14 days, with a wide range of 4 to 71 days. Unfortunately, overall mortality at 30 and 90 days was 30%–40%. Since the median SOFA score of 5 and SAPS II score of 34 predict approximately a 5%–15% mortality rate, these poor outcomes despite treatment with a first-line β-lactam agent are disappointing.

Not surprisingly, patients with cUTIs had the best outcomes (4/4 treatment success), while outcomes for other infections were considerably worse (7/10 success with bacteremia, 6/12 for pneumonia, 5/11 for other). Adding to concerns about how to dose the drug in the setting of renal failure, patients receiving continuous renal replacement therapy had significantly worse outcomes. However, cohorts stratified by creatinine clearance were small, and no apparent relation between creatinine clearance and outcome was seen.

Unfortunately, there was an alarmingly high rate (24%) of relapse from CRE after completion of therapy, and 1 patient developed recurrent urinary colonization but not infection. Of utmost concern is that 3 of these patients (8% of the entire cohort) developed reinfection by a strain that had developed resistance (MIC ≥ 16 µg/mL to ceftazidime-avibactam following only 10–19 days of therapy. These results may bode very poorly for the sustainability of ceftazidime-avibactam for such complicated infections; new therapies for KPC strains may soon be needed. From a scientific standpoint this was predictable—laboratory investigation demonstrated that resistance to ceftazidime-avibactam can arise as the KPC β-lactamase becomes more of an ESBL [18].

There was no apparent efficacy advantage to combination therapy. None of the patients whose strains developed resistance to ceftazidime-avibactam were treated with combination therapy; however, given the small sample size, this may be random chance. Whether combination therapy can be used to prevent emergence of resistance to ceftazidime-avibactam in CRE is not known. For gram-negative bacteria generally, the results of studies of combination therapy to reduce the emergence of resistance have been mixed [19, 20]. Also, we do not know which combinations show more promise in slowing the emergence of resistance, if it can be slowed. There is a critical need for new approaches to prevent the emergence of resistance, and truly novel approaches would be welcomed.

It is important not to draw firm conclusions from an uncontrolled, retrospective case series. Nevertheless, this is a very important study, as it is the first meaningfully clinical evaluation of the efficacy of ceftazidime-avibactam when treating CRE infections, and among a fairly large number of patients with CRE. The results are quite concerning. Mortality continues to be high, and resistance seems to emerge rapidly.

In the movie Jaws, after confidently setting out with an experienced shark-hunter, upon catching his first glimpse of the predator, Chief Brody famously uttered, “We’re gonna need a bigger boat.” Similarly, we rejoiced at our triumph when ceftazidime-avibactam became available to treat our patients infected with KPC-producing bacteria, and we confidently set out to combat this killer. But like the Chief, we appear to have underestimated our foe. We, too, need a “bigger boat.”

We must not let the past repeat itself. Hubris about the sudden availability of effective antibiotics has led to overconfidence and complacency among the medical and microbiological communities on several occasions in the last 80 years, with serious societal consequences [8, 9, 21–23]. Shields and colleagues have provided us a sobering reminder that there is no endpoint in our struggle against microbes. They will never stop adapting to what we conceive of to combat them, and, in turn, we must never stop conceiving of new ways to stay one step ahead.

Notes

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