Ceftazidime-Avibactam and Carbapenem-Resistant Enterobacteriaceae: “We’re Gonna Need a Bigger Boat”

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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 integron-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 for 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 there are 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 en-
countered (n = 29), with the remainder
comprised of ceftoxime-munich, oxacil-
linase, sulfhydryl variable, and AmpC
ESBLs. Metallo-β-lactamases were not
encountered.

Ceftazidime-avibactam was predomi-
nantly 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 me-
dian SOFA score of 5 and SAPS II score
of 34 predict approximately a 5%–15% mortality rate, these poor outcomes de-
spite treatment with a first-line β-lactam
agent are disappointing.

Not surprisingly, patients with cUTIs
had the best outcomes (4/4 treatment suc-
cess), while outcomes for other infections
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how to dose the drug in the setting of
renal failure, patients receiving continuous
renal replacement therapy had signifi-
cantly worse outcomes. However, cohorts
stratified by creatinine clearance were
small, and no apparent relation between
creatinine clearance and outcome was
seen.

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high rate (24%) of relapse from CRE after comple-
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cation (MIC) of 1 (0.25–4) µg/mL to ceftazidime-avibactam, with a median

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 ut-
terred, “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 un-
derestimated 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 overconfi-
dence and complacency among the medi-
cal and microbiological communities on
several occasions in the last 80 years,
with serious societal consequences [8, 9,
21–23]. Shields and colleagues have pro-
vided us a sobering reminder that there
is no endpoint in our struggle against mi-
crobes. They will never stop adapting to
what we conceive of to combat them,
and, in turn, we must never stop conceiv-
ing of new ways to stay one step ahead.

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References
1. Spellberg B, Slaes D. Prioritized current unmet
needs for antibacterial therapies. Clin Pharmacol
Ther 2014; 96:151–3.
US Centers for Disease Control and Prevention. Available at:
cessed 15 August 2016.
3. Infectious Diseases Society of America. White Paper. Recommen-
dations on the conduct of superiority and organ-
ism-specific clinical trials of antibac-
terial agents for the treatment of infections caused
by drug-resistant bacterial pathogens. Clin Infect
4. Gasiuk LB, Edelstein PH, Lautenbach E, Synnest-
veldt M, Fishman NO. Risk factors and clinical impact of
Klebsiella pneumoniae carbapenemase-producing
K. pneumoniae. Infect Control Hosp Epidemiol
5. Schwaber MJ, Carmeli Y. Mortality and delay
in effective therapy associated with extended-
spectrum beta-lactamase production in Enterobac-
teraceae bacteriemia: a systematic review and


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