The Real Crisis in Antimicrobial Resistance: Failure to Anticipate and Respond

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Encountering multidrug-resistant (MDR) Gram-negative infections in critically ill patients has become an all-too-common occurrence in healthcare settings. Increasingly, clinicians are faced with pathogens that are “untreatable,” forcing them to design or implement novel or unproven combinations of antibiotics to address treatment dilemmas. In most cases, these untreatable pathogens possess a wide variety of resistance determinants that when combined create an “antimicrobial resistance nightmare”. Notably, the most problematic phenotypes include carbapenem resistance mediated by the expression of metallo-β-lactamases (eg, NDM, IMP, VIM, or L1) and/or serine carbapenemases (eg, KPC, OXA-23, OXA-24, or OXA-48). Oxyimino-cephalosporin resistance can be manifested in Gram-negative bacteria by inducible chromosomal cephapirinoses (eg, AmpC like P99 and CMY-2) and extended-spectrum β-lactamases (eg, CTX-M-15 ESBLs). In the company of numerous aminoglycoside modifying enzymes, altered penicillin binding proteins, upregulated efflux pumps, target site modifications, membrane changes, and porin deletions, some bacteria are resistant to all known antibiotics. This is not a new story; it is just becoming more and more frequent.

The Infectious Diseases Societies of Europe (European Society of Microbiology and Infectious Diseases [ESCMID]) and the United States (Infectious Diseases Society of America [IDSA]) recognize this crisis and have wisely created Guidelines and Guidance to assist clinicians [1, 2]. The pharmaceutical industry is also trying to assist and meet this challenge with the promise and intense development of new broad-spectrum therapeutic agents that will overcome these MDR pathogens. The most aggressive and forceful therapeutic development so far has been in the area of β-lactam and β-lactam/β-lactamase inhibitor combinations. Fortunately, some have been approved (eg, ceftazidime/avibactam, imipenem/relebactam, meropenem/vaborbactam, cefotolozane/tazobactam, and sulfactam/durlobactam), and many are in or completed Phase III trials (eg, ceftepime/taniborbactam, cefepime/zidebactam) and will soon be ready for regulatory agencies to evaluate and hopefully for clinicians to use. Other promising therapeutics are on the horizon as well (eg, cefiderocol/xeruburbactam and cefepime/enmetazobactam). Agents that are improvements of the existing aminoglycoside and tetracycline classes, such as eravacycline, omadacycline, and plazomicin, could also potentially play a role. We will anxiously await the progress of Zosuquilbin as it makes its way to clinical trials [3]. As is widely recognized, getting a new antibiotic to market is not easy, guaranteed, or profitable in our current economic climate [4]. It is also very difficult to find an appropriate role for some of these agents. Most concerning is the accelerated development of resistance to novel agents that may not follow previously established patterns (Figure 1). We are now observing that resistance to more recent antibiotics introduced into the clinic is present before their commercial release [5–14].

In this issue of Clinical Infectious Diseases, we encounter a tragic case report that challenges even our best efforts. In brief, Dr Senchyna and coauthors from the clinical microbiology laboratory of Dr Niaz Banaei at Stanford Hospital recount a fatal case of relapsing NDM-producing Escherichia coli bacteremia in a severely immunocompromised 12-year-old child. Blood cultures were positive on initial evaluation and on hospital days 26 and 36. A venous catheter for hemodialysis access was implicated, and a PICC was placed while the patient was bacteremic; both were eventually
removed on hospital day 26. The initial bacteremia responded to the combination aztreonam plus ceftazidime/avibactam at recommended doses, as suggested by expert guidance from both IDSA and ESCMID as a treatment option for MBL-producing Enterobacteria [1, 2]. Careful microbiological testing was also performed demonstrating activity of aztreonam and

Figure 1. A, The previous paradigm in the development of antibiotic resistance. Antibiotics are developed and then resistance is reported. B, The current paradigm in antibiotic resistance. Drug resistance is discovered and detected while the antibiotics are in the preclinical development phase. Abbreviations: PDR, pan drug resistance; XDR, extreme drug resistance.
ceftazidime/avibactam. Fortunately, new microbiological testing guidance have just been approved by the Clinical and Laboratory Standards Institute (CLSI) so that clinicians can determine if this is a potentially appropriate choice for their patients [14]. In choosing this therapy, the treating team rightly considered that although observational studies report almost 80%–90% treatment response with this combination [15, 16], a prospective randomized clinical trial to confirm that this combination is the optimal choice for the treatment of MBL-producing Enterobacteria does not yet exist. Moreover, extrapolating from results of clinical trials conducted with aztreonam/avibactam that are still in progress may never be determined. One worries that, as shown in microbiological evaluation and in hollow fiber models of infection, the use of ceftazidime/avibactam with aztreonam may provide a more durable response than aztreonam and avibactam alone [17].

As reported, 3 sequential isolates were analyzed in the process and the assertion is made that in the prolonged courses of treatment, isolates 2 (resistant to ceftazidime, ceftazidime/avibactam, and aztreonam) and 3 (resistant to ceftazidime and cefiderocol; ceftazidime/avibactam and aztreonam not tested) independently evolved from isolate 1. What did these investigators find that undermined their therapy? An elegant, detailed, and truly frightening genetic description is offered. The main findings are:

1. Isolate 1 (pre-treatment!) carried a pre-existing 4 amino acid insertion (Tyr-Arg-Ile-Lys) at amino acid position 333 of PBP3 which conferred resistance to aztreonam, but also mediates reduced susceptibility to cefiderocol [12, 18, 19]. Ceftazidime has a high affinity for PBP3 and moderate affinity for the PBP1a of certain Gram-negative organisms, such as E. coli. Aztreonam is relatively PBP3 specific. The combination of ceftazidime/avibactam and aztreonam may completely affect the “divisome” of Gram-negative bacteria and have an independent impact on its own [20]. But signals that this combination could potentially fail were evident even 6 years ago when its promise was first reported [20, 21]. A tetrapeptide insertion in the E. coli PBP3 was found to diminish the impact of aztreonam added to ceftazidime/avibactam [21]; higher amounts of aztreonam were required to lower minimum inhibitory concentrations (MICs) to the triple combination [20].

2. Expression of NDM-5, a metallo-β-lactamase that is often found with other genetic mutations (see below) that confers cefiderocol resistance. In this case, the NDM-5 gene was found as a single copy, in contrast to other reports [22]. NDM-5 (2 substitutions different from NDM-1, V88L and M154L) is unique in that it is among the NDM variants that tolerates zinc deprivation, a critical trait for MBL activity in sites of infection [23, 24]. It is also the most widespread variant of NDM-1 currently reported.

3. A stop codon in the siderophore (iron) receptor CirA. This stop codon in CirA impairs cefiderocol transport into the bacterial periplasmic space thus preventing entry into bacteria and stopping the inactivation of PBPs. The presence of NDM-5 and cirA mutations both contribute to cefiderocol resistance [19, 25, 26]. Understanding of the synergy between these 2 resistance mechanisms against cefiderocol, and the presence of multiple-copy plasmids, remains to be further studied.

4. Mutation in the multidrug efflux resistance nodulation-cell division (RND) transporter permease AcrD and a second mutation in the multidrug efflux major facilitator superfamily (MFS) transporter periplasmic adaptor subunit EmrA, known to export multiple classes of antibiotics, were detected. The exact role here is a little unclear but likely contributes to the observed phenotypes. Further studies using knockouts or knockdowns in isogenic strains are needed.

**WHAT SHOULD CLINICIANS TAKE FROM THIS?**

Based upon currently available evidence, the choice of antibiotics was sound. In each case, the treating team executed “precision infectious disease treatment” to address the multidrug-resistant organism they encountered. Careful microbiology and clinical decision making were evident, and these authors need to be recognized for their expert care. However, it is truly unclear if other agents should have been added to reinforce the potent action of the drugs used. Sometimes, administering antibiotics that have a different mechanism of action could complicate the clinical situation by providing antagonism. Furthermore, we are uncertain that adding more agents to existing susceptible regimen improves outcomes. In this case, likely because high concentrations of aztreonam were being achieved, the triple regimen was adequate for 26 days. One wonders if the immunosuppressed status of the host and retention of the hemodialysis catheter contributed to treatment failure and led to the breakthrough bacteremia on hospital day 26. As clinicians, we should also remember with humility the “90-60 rule”: infections due to susceptible isolates respond to therapy approximately 90% of the time, whereas infections due to resistant isolates respond approximately 60% of the time [27]. As we were reminded by a recent randomized controlled trial of complicated *Staphylococcus aureus* bacteremia, a more commonly encountered and yet serious infection, overall treatment success with active antibiotics only occurs in 70% of cases [28].

**Why did Things go Wrong?**

We have learned time and time again that the evolution of resistance is inevitable. Even though these are very potent drugs, like antibiotics that preceded them, we should anticipate failure. We no longer
have the luxury of waiting years for resistance to emerge to a specific drug. In fact, we now know that resistance can be demonstrated to even the most potent agents before they are even released [5–14]. This “collateral damage” is an inevitable result of years and years of indiscriminate antibiotic use and also of the “resitome” developed and shared by microorganisms over millennia, before the clinical use of antibiotics [29]. Despite stewardship efforts and strict control of formularies that mitigate the evolution of these superbugs, we seem not to be able to stop these sentinel events from happening.

What Does This Mean?
Simply put, we are losing the battle. We are failing to properly anticipate the evolution of these multidrug-resistant pathogens. Preclinical investigations to see how resistance will evolve should be accelerated as they can be lifesaving. If clinicians are informed of the possible mechanisms whereby resistance will emerge, even if it is laboratory based, preventive measures can be employed to discover and detect a possible treatment failure. “Antibiotics live and die at the bench.”

What Can we Do About it?
We need to respond faster. These MDR organisms are “paying it forward,” and our antibiotic research community is not keeping up. The following items are proposed.

1. Experiments need to be designed (and supported!) to explore all avenues of resistance to currently available and newly designed antibiotics. Defining what resistance mechanisms result in “untreatable” phenotypes will permit us to anticipate what we will be up against. As a result, we will also need to provide laboratories with the resources to contain these “gain of function” pathogens that are discovered [30]. This offers an opportunity for industry and academic partnerships to be created that can have very beneficial effects for our patients who will receive these drugs.

2. In very complicated cases encountered in the clinic such as this, we should be employing rapid molecular diagnostics and whole genomic sequencing of the infecting organisms in “clinical real time” to monitor and adjust treatment. This may not be as expensive as feared if done on a regional or centralized basis. Standards can be developed, and sentinel laboratories can be designated that can process these genetic analyses quite quickly and inexpensively.

3. We still need to “rethink” how we do clinical trials and that we need to re-vize the timeline of introducing new pharmaceutical agents into the therapeutic pipeline. Basically, we need to act faster despite some uncertainties. These organisms are living in a much faster timeline and are evolving very quickly. Does it really need to take years to bring a new (and safe) drug to the clinic? Can we compress further the standard milestones that need to be achieved? Can we enroll more patients pragmatically? Even saving 2 years would be a big help!

4. Can we develop regional antimicrobial stewardship programs and surveillance networks that address the pathogens described in this study. Presently, each hospital has its own stewardship program, yet our patients travel from one facility to another and cross state lines. Breaking down economic and territorial barriers would go a long way to help our patients.

Our current approach regarding the development of new therapies and emergence of resistance is clearly based on “older models.” We advocate to embrace a “quantum approach” and recognize that we need to anticipate change and respond along a different timeline. The MDR pathogens are a real crisis, and not acting faster may be a bigger problem. To quote Dr. Peter Piot, there is “No time to lose.”

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