EDITORIAL COMMENTARY

Polymyxin-Resistant *Acinetobacter baumannii*: Urgent Action Needed

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(See the Major Article by Qureshi et al on pages 1295–303.)

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In 2009, the Infectious Diseases Society of America (IDSA) set the acronym ESKAPE, which lists the groups of pathogens that pose the highest threat to patients' safety and to public health [1], one of which is *Acinetobacter baumannii* [1]. *Acinetobacter baumannii* is a particularly challenging pathogen because it is associated with a high degree of resistance [2], and it is difficult to eliminate its environmental reservoir in healthcare settings with conventional measures [3]. Carbapenems are considered first-line agents for the treatment of *A. baumannii* infections [4–6], and therefore the rise of infections due to carbapenem-resistant strains is of particular concern, as outcomes deteriorate significantly when isolates become resistant to all β-lactam options [2, 3, 5–7]. Additionally, carbapenem-resistant *A. baumannii* isolates are often susceptible to only 1 or 2 agents, making them extensively drug-resistant (XDR) pathogens by definition [8]. The incidence of XDR *A. baumannii* infections is continually rising [9]. For severe XDR *A. baumannii* infections, polymyxins are frequently used, and are considered by most to be the drugs of choice [4]. In this issue of *Clinical Infectious Diseases*, Qureshi and colleagues report on a case series of patients with isolation of colistin-resistant carbapenem-resistant *A. baumannii* [10]. In some of the cases described by the authors, the isolates have become truly pandrug resistant (PDR) with resistance seen to all tested antimicrobials. These infections represent a serious iatrogenic complication of modern healthcare, where patients acquire infections in our healthcare facilities, for which we have no treatment options.

WHAT ARE OUR OPTIONS FOR TREATING INVASIVE XDR *A. BAUMANNII* INFECTIONS?

XDR *A. baumannii* invasive infections are frequently managed with polymyxins [4, 11]. If polymyxins are not an option due to resistance or toxicity, the most active agent is often tigecycline, but unfavorable pharmacokinetics leading to suboptimal concentrations in the blood and epithelial lining fluid with current dosing strategies [12] make it less than ideal for the treatment of bloodstream or respiratory tract infections. Minocycline also has excellent in vitro activity against XDR *A. baumannii*, and potentially offers more favorable serum concentrations [13]; however, clinical experience is limited [13]. Although select aminoglycosides might also retain activity, the utility of these agents as monotherapy outside of the urine is controversial, and current evidence does not support their use [14]. Interestingly, sulbactam can retain activity, even in XDR *A. baumannii*. Unfortunately, however, optimal use and dose of sulbactam remain unclear, it is not routinely available or tested in many institutions, and the only patient in this case series who received monotherapy with the agent died despite in vitro susceptibility.

EPIDEMIOLOGICAL SIGNIFICANCE OF POLYMYXIN-RESISTANT *A. BAUMANNII* INFECTION

Clinical findings of infections caused by polymyxin-nonsusceptible isolates have been reported with other gram-negative pathogens, including Enterobacteriaceae [15–17] and *Pseudomonas aeruginosa* [18]. This US study [10] could now be added to previous reports of polymyxin-

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resistant *A. baumannii* from other parts of the world [19–27]. Most case-series analyses point having a tendency to population of patients who are frequently old, institutionalized, and debilitated [10, 23]. However, a consistent risk factor, which stands out in Qureshi et al's report [10] and others' [15–17, 28, 29], is recent exposure to polymyxins. The fact that 19 of the 20 patients in this report were recently exposed to colistimethate sodium warrants particular attention. Although the authors do not describe how colistin was given (ie, dose, duration, as monotherapy vs combination therapy), suboptimal use of this agent might have contributed to the development of these resistant isolates, and stresses the urgent need for data demonstrating the optimal method of polymyxin administration. The clear association manifested in this [10] and other reports [15] should prompt immediate action to contain inappropriate usage of polymyxins. Polymyxins should not be used to try and decolonize asymptomatic carbapenem-resistant Enterobacteriaceae (CRE) carriers [30] or be delivered as part of selective oral or selective digestive decontamination protocols [31]. Even the empiric parenteral usage of polymyxins should be subjected to tight restrictions and regulations. This recommendation should always be weighed against the fact that when polymyxins are indicated (as the only appropriate therapeutics for XDR gram-negative infections), they are usually administered too late during the course of the disease, with a median delay of up to 5 days [11]. This delay unfavorably impact patient outcomes, as time to appropriate therapy is the strongest independent predictor for mortality in severe sepsis [32].

HOW DO *A. BAUMANNII* STRAINS BECOME RESISTANT TO POLYMYXINS?

Polymyxins act on the outer membrane of *A. baumannii* through electrostatic interactions between the positive charge of the five Dab residues of the polymyxin molecule and the negatively charged phosphate group on the lipid A moiety of the lipopolysaccharide (LPS) [33]. The mechanisms of resistance to polymyxins in *A. baumannii* are usually through modifications of the lipid A component [23]. Complete removal of LPS has been reported [34, 35], either by inactivation of certain biosynthesis genes (eg, lpxA, lpxC, lpxD) [34], or through certain insertion sequences (eg, ISAba11) [36]. Phosphoethanolamine added to hepta-acylated lipid A may also lead directly to polymyxin resistance [37]. All these mechanisms result in polymyxin resistance by reducing the net negative charge of the outer membrane, thus reducing the affinity of polymyxin to the bacterial surface [38]. In the article by Qureshi et al [10], phosphoethanolamine modifications of lipid A were present among all colistin-resistant *A. baumannii* isolates.

IS THERE HELP ON THE HORIZON?

The pipeline of new molecules for treating XDR gram-negative bacteria is limited, and this is particularly true with regard to agents with activity against *A. baumannii*. Encouragingly, there has been a marked increase in the number of novel gram-negative agents that have made it to phase 2 or beyond in response to the 2009 IDSA campaign [1]. In 2012, President Obama signed into law the Generating Antibiotic Incentives Now act, which allowed antibiotics treating life-threatening antibiotic-resistant infections to be designated as "qualified infectious disease products" (QIDPs). This allowed a new product fast-track status, priority review, and additional 5-year exclusivity free from generic competition. This law has shown early success as 2 new antibiotics against gram-negative bacteria have been recommended for approval. The first, ceftolozane-tazobactam, recently received full US Food and Drug Administration approval, and a final decision on ceftazidime-avibactam is expected in the first quarter of 2015. Although these agents will be significant advancements in the treatment of XDR *P. aeruginosa* and CRE, neither has appreciable activity against carbapenem-resistant *A. baumannii* [39, 40]. Two other agents in phase 3 development, plazomicin and carbavance (meropenem/RPX7009), also have a heavy focus toward CRE [41, 42]. Whereas plazomicin appears to be more potent than other available aminoglycosides against *A. baumannii*, 50% of minimal inhibitory concentration (MIC_{50}) and 90% of minimal inhibitory concentration (MIC_{90}) values remain high (8 and 16 mg/L, respectively) [43], and as previously discussed, the role of aminoglycosides as monotherapy for systemic infections is controversial. RPX7009 is a novel boronic acid inhibitor with potent class A and C β-lactamase inhibitory properties. However, it does not restore the activity of the carbapenem in carbapenem-resistant *A. baumannii*, where class D oxacillinases are the predominant resistance mechanism [44]. Additionally, relebactam combined with imipenem-cilistatin was recently granted QIDP status, and phase 3 studies should commence early in 2015. However, relebactam will not restore carbapenem activity against *A. baumannii* [44].

However, it is not all bad news. A novel fluorocycline, eravacycline, is currently in phase 3 development, and has shown potent in vitro activity against carbapenem-resistant *A. baumannii*, with MIC_{50} and MIC_{90} values slightly lower than those of tigecycline (0.5 and 2 μg/mL vs 2 and 8 μg/mL, respectively) [45]. Limited pharmacokinetic data suggest the potential for enhanced epithelial lining fluid penetration with eravacycline [46], but its role for invasive *A. baumannii* infections remains to be seen. A bit further down the pipeline, S-649266, a siderophore cephalosporin, has shown activity in *A. baumannii* including carbapenem-resistant strains. Data showed MIC_{50} and MIC_{90} values in 102 *A. baumannii* isolates to S-649266 of 0.125 and 2 mg/L,

respectively, even in the setting of MIC_{50} values to meropenem of >16 μg/mL [47].

CONCLUSIONS

Qureshi et al's meticulously executed matched analysis [10] should prompt close attention to the impending challenge posed by polymyxin-resistant, carbapenem-resistant *A. baumannii* infection dissemination. Because highly effective alternative therapeutics are not yet available, nor will they be in the immediate near future, patients with this infection are frequently managed with various combinations of drugs without strong data to support these practices. Of the 20 patients reported by Qureshi and colleagues, the mortality rate of these frequently PDR infections was "only" 30%, with 15% only colonized, not truly infected [10]. This might relate to virulence and fitness properties of these currently disseminating strains [48]. Regardless, to handle this threat, selective pressure imposed through inappropriate polymyxin usage should be reduced through standardizations of prescribing policies, and optimizing exposures when polymyxins are warranted. Innovative predictive measures (eg, specified prediction tools) and implementing rapid diagnostic techniques could shorten the time to initiation of polymyxins in the population that would truly benefit from their earlier initiation, while limiting exposure in those who would not. Patients colonized with polymyxin-resistant *A. baumannii* should be subjected to enhanced infection control measures to prevent its continued spread, and should not be cohorted with carriers of other XDR ESKAPE pathogens [49].

Note

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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