The New Acinetobacter Equation: Hypervirulence Plus Antibiotic Resistance Equals Big Trouble

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(See the Major Article by Jones et al on pages 145–54.)

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Acinetobacter baumannii is well known to clinicians as a cause of healthcare-associated infections [1]. Although biochemically indistinguishable from A. baumannii, Acinetobacter pittii and Acinetobacter nosocomialis are more recently described species that may also cause healthcare-associated infection and form part of the A. baumannii “complex.” The typical antibiotic-resistance phenotype of A. baumannii and related species in most hospitals is now one of resistance to carbapenems and numerous other antibiotic classes. In many cases, A. baumannii is extensively drug resistant (XDR), implying susceptibility to only 1 or 2 antibiotic classes. XDR A. baumannii is typically clonal, with about 50% of cases worldwide being part of the international clonal complex II [1]. Although frequently causing colonization of the respiratory tract, clinically significant infections are seen, especially in compromised patients. While mortality attributable to XDR A. baumannii certainly occurs, mortality is often a result of underlying disease. Acinetobacter baumannii is rightly described as generally being a low-virulence organism.

The significance of the report by Jones and colleagues in this issue of Clinical Infectious Diseases [2] lies in its demonstration of healthcare-associated A. baumannii infections being due to highly virulent pathogens, with consequent death of patients with relatively minor underlying disease (Table 1). In this report, 6 patients from the northwestern United States who died from healthcare-associated XDR A. baumannii infections are described. Two clades are described—one belonging to the geographically widespread international clonal complex II (and sequence type 2) and the other belonging to the relatively uncommon sequence type 10. The rarity of this second clade, which predominated in the outbreak, is indicated by its unique pulsed-field gel electrophoresis pattern among 1800 A. baumannii isolates in the Walter Reed Army Institute of Research collection. The clade was extensively drug resistant, with 21 antibiotic-resistance genes being detected. Worse still, representative isolates of this clade were highly virulent in a mouse model and possessed a unique combination of virulence genes. This included a novel gene cluster encoding enzymes for protein glycosylation, which is a process known to play a key role in virulence determinants such as biofilm formation or capsule production.

Jones and colleagues should be commended for their multifaceted approach to the outbreak investigation, including comparative genomics and animal models of virulence to complement the clinical and microbiological data. The application of whole genome sequencing not only

<table>
<thead>
<tr>
<th>Feature</th>
<th>Jones et al [2]</th>
<th>Typical strains</th>
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<tbody>
<tr>
<td>Geographic locale</td>
<td>Northwestern United States</td>
<td>Worldwide</td>
</tr>
<tr>
<td>Belongs to international clonal complex</td>
<td>No (ST10)</td>
<td>Typically</td>
</tr>
<tr>
<td>Carbapenem resistant</td>
<td>Sometimes</td>
<td>Frequently</td>
</tr>
<tr>
<td>Mechanism of carbapenem resistance</td>
<td>Porin loss; no carbapenemase</td>
<td>Carbapenemase (typically)</td>
</tr>
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<td>Virulence</td>
<td>Highly virulent</td>
<td>Low virulence</td>
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helped elucidate the suite of resistance or virulence genes accounting for the phenotype but also provided some insight into how the A. baumannii outbreak clade may have evolved. The isolates contained a unique variant of the gene cluster encoding a type VI secretion system (a specialized needle-like apparatus used to transport proteins into other cells) with varying degrees of gene deletion, resulting in complete loss of genes in strains isolated up to 1 year after the outbreak began. This could reflect adaptation to the human host or immune evasion over time as the genome responded to selection pressures by discarding “costly” genes that are less critical in a niche without competing microorganisms, highlighting the ability of A. baumannii to rapidly respond to changing environments.

Clinicians need to be aware of this combination of hypervirulence and extensive drug resistance. Certainly, examples of seemingly higher-virulence A. baumannii isolates have occurred. In tropical areas of the world, community-acquired pneumonia due to A. baumannii does occur, especially during seasons with high rainfall. In one case series of 41 patients with bactereemic community-acquired pneumonia due to A. baumannii, 80% of patients required admission to an intensive care unit [3]. The complete genome of such community-acquired strains has been analyzed, revealing numerous additional gene clusters compared with previously sequenced hospital-acquired strains [4]. However, notably absent from the community-acquired strains were antibiotic-resistance islands, leaving these isolates typically susceptible to carbapenems and other beta-lactam antibiotics [4].

Examples of likely higher-virulence healthcare-associated A. baumannii isolates have also occurred. For example, a healthcare worker became seriously ill with A. baumannii after endotracheally suctioning a patient with A. baumannii infection [5]. Fulminant sepsis due to carbapenem-resistant isolates belonging to international clonal complex II has been well described [6]. Animal studies indicate that highly virulent strains can establish very high early bacterial loads in the blood, most likely by way of being resistant to early innate effectors [7]. Sustained bacteremia may then occur, leading to Toll-like receptor 4–mediated hyperinflammation [7] and subsequent death.

Although mortality from A. baumannii may arise in hypervirulent strains despite appropriate empiric antibiotic therapy, optimal outcomes are likely to be associated with early, highly effective therapy. XDR A. baumannii strains may only be susceptible to polymyxins or tigecycline. Resistance to polymyxins and tigecycline is now well reported, and a truly pan-drug-resistant (PDR) strain has been described [8]. What is in the pipeline for Acinetobacter? Two newly approved antibiotics, ceftolozane–tazobactam and ceftazidime–avibactam, are unlikely to provide significant advantages for treatment of XDR or PDR A. baumannii strains. Of antibiotics under development, evacycycline [9] or siderophore antibiotics, which rapidly penetrate Acinetobacter’s outer membrane [10], may be the most effective new treatment options in the next decade.

Vaccination against A. baumannii is being developed, as are new rapid diagnostic tests. Yet, at the present time, our best defense against hypervirulent XDR A. baumannii strains such as those described by Jones and colleagues [2] remains old-fashioned, stringent infection control measures combined with the application of effective antimicrobial stewardship.

Note

Potential conflict of interest. D. L. P. has received honoraria for advisory board participation from AstraZeneca, Cubist, Merck, Pfizer, Shionogi, and Leo Pharmaceuticals. Other authors report no potential conflicts.

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References