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The Deadly Impact of Extreme Drug Resistance in *Acinetobacter baumannii**

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Infections caused by *Acinetobacter* species, and by *Acinetobacter baumannii* in particular, began to emerge in the 1960s and 1970s, driven by the development of modern intensive care medicine, including mechanical ventilation, central venous and urinary catheterization, and intensive antibacterial therapy (1–4). Antibacterial therapy wipes out normal flora, enabling resistant *Acinetobacter* to thrive, while insertion of foreign bodies enables the organism to bypass anatomical barriers it would not normally be able to penetrate. Even as these infections continued to increase in frequency through the 1980s and 1990s, *Acinetobacter* was often considered to be of low virulence potential, and mortality was often attributed to patients' underlying disease, rather than to the infection itself.

However, as far back as 1977, mortality rates of nosocomial pneumonia caused by *A. baumannii* were described to be very high for patients who received inadequate therapy compared with those who were treated adequately (1). These results hinted that the true virulence of the pathogen might have been obscured by the availability of adequate therapy. Similarly, for many years, the impact of ventilator-associated pneumonia (VAP) on mortality generally was underappreciated, with a common expression being that patients “die with VAP, rather than of VAP.” Patients with adequately treated VAP often die of their underlying diseases (5); however, recent analyses comparing the mortality rate of VAP treated with initially effective versus ineffective therapy have determined that initially effective therapy reduces mortality of VAP by at least 30% (6–8). These results underscore a critically important concept: effective antibiotic therapy can mask the virulence of microbes by greatly improving outcomes of infection irrespective of pathogenic potential of the organisms. Such virulence is unmasked in settings where inadequate therapy is not administered in a timely manner.

It is in this context that the dramatic rise in the prevalence of carbapenem-resistant *Acinetobacter* is of substantial concern. Recent data from a national surveillance of hospitals in the United States revealed that more than 50% of *A. baumannii* isolates from ICUs are now carbapenem-resistant (9). Internationally, carbapenem-resistance rates among *A. baumannii* are described that are even higher (10, 11). This rise in extreme drug-resistant strains, which tend to be treatable only with polymyxins or tigecycline, has been accompanied by an alarming rise in the mortality of resulting infections (12–16). In this issue of *Critical Care Medicine*, Lee et al (17) now add important new data that underscore the deadly impact of carbapenem resistance in the context of bacteremia and help explain why it contributes to excess mortality.

The authors present a well-controlled and very large retrospective study to evaluate determinants of mortality in patients with bacteremia caused by *Acinetobacter* species in Taiwan. The setting of this study is very unique: the Chang Gang Memorial Hospital is a 3,500-bed tertiary hospital in Taiwan where *A. baumannii* is the most common pathogen for nosocomial bloodstream infection in ICUs. This is not the case for other hospitals—even for many tertiary care centers. Also of note, the identification of the *Acinetobacter* species was done using 16S-23S ribosomal RNA (rRNA) intergenic spacer (ITS) region sequencing. This was done as the taxonomy of the genus *Acinetobacter* is complex. 16S-23S rRNA ITS region sequencing is a more precise identification method for *Acinetobacter* species than routine clinical laboratory identification. Alternatively, a 350-bp highly variable zone on the *rpoB* gene is also reliable target for rapid molecular identification called “partial *rpoB*” sequencing (18). It must be stressed that the proper identification of *Acinetobacter* species, including those within the *A. baumannii* group, is required to increase our knowledge of the epidemiology, pathogenicity, and clinical impact of the various species of this diverse genus (19). This may be a requirement for all clinical studies looking at outcomes of *Acinetobacter* infection.

The overall mortality (33%) of these infections underscores their severity. Patients infected with carbapenem-resistant strains, which constituted 30% of the cohort, had similar underlying diseases compared with patients infected with carbapenem-susceptible strains. However, infections caused by carbapenem-resistant *Acinetobacter* had a frighteningly high 70% mortality rate compared to a 25% mortality rate caused by susceptible bacteria.

The carbapenem-resistant isolates were extraordinarily resistant to other antibiotics as well. Only tigecycline (23% resistance) and colistin (no resistance detected) remained reliably active. These findings account for the fact that only 28% of infections caused by carbapenem-resistant *Acinetobacter* were treated with an active antibacterial agent within the first 48 hours when compared with 67% of the infections caused by carbapenem-susceptible isolates. Receipt of initially effective therapy was a primary driver of outcome, reducing 30-day mortality from 60% without to 20% with effective therapy. When only analyzing infections caused by carbapenem-resistant isolates, treatment with tigecycline or colistin within 48 hours markedly reduced death compared to receipt after 48 hours (mortality rates, < 38% vs > 88%). Since it can take 48–72 hours to determine the identity of the pathogen and its susceptibility profile from blood cultures, it is critical that empiric

therapy used to treat infections that may be caused by carbapenem-resistant *A. baumannii* include a polymyxin or colistin.

The authors of this analysis found that the impact of carbapenem resistance on mortality was driven by the increased frequency with which initially ineffective therapy was administered to such patients. That is, carbapenem-resistant *Acinetobacter* isolates did not appear to be more virulent than susceptible isolates, nor did patients infected with carbapenem-resistant isolates inherently have more severe underlying diseases. They were simply more difficult to treat appropriately.

The primary limitations of the study were its single-center design, with unique microbiology in that center, and retrospective nature. Nevertheless, the results are consistent with prior studies of initially ineffective therapy for VAP caused by *A. baumannii* (20–24). Furthermore, the microbiology and resistance mechanisms encountered were not unique or unusual.

As resistance rates continue to rise, clinicians will increasingly encounter infections caused by carbapenem-resistant *Acinetobacter*. The current data underscore the lethality of infections caused by these strains. In healthcare systems and individual ICUs where carbapenem-resistant *Acinetobacter* infections are encountered, early initiation of regimens including polymyxins or tigecycline is critical to improving survival. The results also emphasize the need for more effective antibiotic stewardship programs to minimize patient exposure to therapy with broadly active antibacterial therapy that selects for carbapenem resistance. Finally, the antibacterial pipeline remains dangerously thin for agents that have activity against carbapenem-resistant *Acinetobacter*. Novel infection prevention technologies and novel therapeutics are critically needed for these infections (25).

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