Multidrug-resistant *Acinetobacter baumannii*: "Eyes Wide Shut"?

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At present, *Acinetobacter baumannii* is one of the most important nosocomial pathogens. Its ability to colonize hospitalized patients and survive on inanimate surfaces for prolonged periods of time has contributed to its rapid success in the hospital.[1] In addition, its unique ability to develop and demonstrate resistance to all known antimicrobial agents makes this a pathogen of singular, contemporary importance.

It is notable that multidrug resistant (MDR) *A. baumannii* is regarded by many clinicians as a "low-virulence" organism that mainly affects severely debilitated patients. As a result the impact of *A. baumannii* in terms of mortality or morbidity is sometimes difficult to demonstrate.[2] Nevertheless, the alarm caused by the emergence and spread of MDR *A. baumannii* through an ICU or hospital should prompt the rapid implementation of aggressive infection control measures. Surprisingly, such programs have not been implemented routinely in many centers. The results of one recent systematic review strongly suggest that infection with or acquisition of *A. baumannii* is associated with increased mortality.[3] Patients infected with MDR strains frequently receive inappropriate treatment and in cases where there is bloodstream infection, the outcomes are poor.[4,5] Additionally, patients colonized or infected by *A. baumannii* also frequently have a prolonged hospital stay, which contributes further to maintaining the reservoir of colonized patients.[6]

Class II carbapenems (imipenem, meropenem) and sulbactam (alone or with ampicillin) are considered the "drugs of choice" for the treatment of severe infections caused by *A. baumannii*.[7] The alternatives for treating infections caused by carbapenem and sulbactam-resistant isolates are very limited, and frequently colistin and tigecycline are the only agents that can be used. The activities of different antibiotic combinations showing possible synergy against carbapenem-resistant strains (regimens that include colistin and rifampin, beta-lactams and colistin, etc.), have been tested *in vitro*, in animal models, and in some observational clinical studies. However, the results of these studies are tentative, our understanding of the biology of *A. baumannii* is limited, and different methodologies are employed. A recent analysis recommended the use of intravenous colistin, rifampin and a carbapenem for infections caused by metallo-beta-lactamase (MBL)-negative, carbapenem-resistant strains, and colistin plus rifampin (with or without tigecycline) for MBL-producing strains.[7] It is certain that as colistin and tigecycline resistant isolates become more prevalent, clinicians will need to reconsider these options.

What is the current situation? In the USA, *A. baumannii* is an increasing cause of nosocomial infection in the intensive care unit (ICU).[8] Outbreaks caused by MDR strains of *A. baumannii* in US soldiers and support personnel wounded during military operations abroad, have recently been characterized.[9,10] In Spain, data from a study carried out in 2000 by the Study Group for Nosocomial Infections (GEIH) in the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), showed that *A. baumannii* was present in most tertiary care institutions.[11] Data from the infection surveillance system of ICU patients (ENVIN-UCI) revealed *A. baumannii* to be the third leading cause of ventilator-associated pneumonia.[12] The median incidence rate for infection (or carriage) in Spanish hospitals in 2000 was 0.22 cases per 1,000 patient-days; in the in the ICU the rate was 1.96.[11] The pooled incidence rate in ICUs between 1997 and 2003 was 1.3 cases per 1,000 patient-days.[13] Unfortunately, carbapenem-resistance is increasing worldwide. In Spain, the situation is particularly frightening. Data from the GEIH study found 41.2% of *A. baumannii* isolates taken during one month in 25 Spanish centers to be imipenem-resistant.[11] These isolates were mainly recovered from hospitals with > 500 beds and from patients with previous antimicrobial treatment or who possessed indwelling urinary catheters and who underwent surgery.[14] One recent study investigated the presence of carbapenemases in these isolates; 100%, 42% and 20% of isolates produced OXA-51-like, 42% OXA-40-like and 20% OXA-58-like enzymes, respectively. IMP or VIM types of MBLs were not detected in any strains.[15] In ICU patients, 35.3% of *Acinetobacter* spp. strains isolated in patients with infections from 1997 to 2003 were imipenem-resistant.[13]

In this issue of *Enfermedades Infecciosas y Microbiología Clínica,* Asensio *et al*. provide useful information about trends in the prevalence of infections caused by carbapenem-resistant *A. baumannii* in Spanish hospitals by analysing data from the EPINE studies (Spanish Study on the Prevalence of Nosocomial Infections).[16] Following a downward trend between 1997 and 2002, they note that carbapenem-resistance has since risen again, reaching 37% in 2005. Another important finding was the significant differences in the proportion of infections caused by carbapenem-resistant isolates from different regions of

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Spain. It would be interesting to discern if there are temporal trends in such differences and whether the results significantly change when adjusted for size of hospital or number of ICU beds. Most notably, 14.6% of infections were considered community-acquired. This should be regarded with caution, since *A. baumannii* has not been described as the clear cause of community-acquired infections in the Western Hemisphere. One wonders if other species of *Acinetobacter* are frequently misidentified by automated phenotypic methods; this could also account for some of these cases. In the GEIH study (which identified all isolates using reference techniques wherein a detailed epidemiological investigation of each case was carried out) only 3.6% of cases were considered community-acquired.[11] Lastly, the assignment of risk factors associated with infection due to carbapenem-resistant isolates may be influenced by unrecognized causes since previous antimicrobial use, a well established association in infections caused by carbapenem-resistant isolates, was not recorded.[14,17]

What are we doing and what should be done? The control of endemic *A. baumannii* is complex and probably requires a deeper knowledge of transmission dynamics.[10] It is necessary that adequate resources be committed to develop specific infection control and investigation programs. It seems paradoxical that these interventions have not yet been advocated by recognized international authorities for this MDR pathogen. Environmental cleaning and disinfection, targeted active surveillance of colonized patients, contact precautions, and prudent antibiotic use are probably the cornerstones for controlling *A. baumannii*.[1,18] It is our opinion that aggressive infection control measures should be applied to all institutions and units caring for patients infected with *A. baumannii* isolates, not only to those harbouring carbapenem-resistant strains. We worry that carbapenem-susceptible clones may easily acquire or express genes conferring carbapenem resistance.

Bergogne-Bérézin warned of the need to control *A. baumannii* in 1995.[19] We have known for more than 10 years that we should keep "our eyes wide open" for *A. baumannii*. Are we devoting enough resources and research to controlling this (and other) MDR pathogens? Are we keeping our "eyes wide shut" in the face of this *A. baumannii* "odyssey" in our hospitals?

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