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Clinical impact and pathogenicity of *Acinetobacter*

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ABSTRACT

Members of the genus *Acinetobacter* have been implicated in a wide spectrum of infectious diseases. Although this organism is associated primarily with nosocomial infections, it has also been involved in cases of community-acquired infection. Before the 1970s, *Acinetobacter* infections were mostly post-surgical urinary tract infections in patients hospitalised in surgical units. The significant improvement in resuscitation techniques during the last 30 years has changed the types of infection caused by *Acinetobacter*. Since the 1980s, *Acinetobacter* has spread rapidly among patients in intensive care units. Today, *Acinetobacter* accounts for *c.* 9% of nosocomial infections, with most *Acinetobacter* infections involving the respiratory tract. Transmission via the hands of hospital staff has become the most important contributory factor in patient colonisation. *Acinetobacter baumannii* is the species that is involved most frequently in infections of humans, but a natural reservoir for *A. baumannii* outside the hospital environment has not yet been identified. Community-acquired infection and infections acquired following war or natural disasters (e.g., earthquakes) have been described. *Acinetobacter* causes mild-to-severe illness, but can be fatal. The severity of *Acinetobacter* infection depends upon the site of infection and the patient's susceptibility to infection as a result of underlying disease. The circumstances that allow *Acinetobacter* to assume a pathogenic role are not really well-understood. As this organism is a low-grade pathogen, the pathogenesis of *Acinetobacter* infections probably involves numerous factors, including virulence determinants, which have yet to be investigated.

Keywords *Acinetobacter baumannii*, clinical impact, nosocomial infection, pathogenesis, review, virulence

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INTRODUCTION

Interest in *Acinetobacter* spp. has been growing for the past 30 years. One of the main reasons for the present increased interest in this genus is the emergence of multiresistant strains, some of which are pan-resistant to antibiotics, that suddenly cause an outbreak of infection involving several patients in a clinical unit [1–3]. There are now >1000 references to 'infections and resistant *Acinetobacter*' in the international scientific literature. Considered to be a commensal, opportunist, relatively low-grade pathogen, *Acinetobacter* was frequently ignored in the 1960s when isolated from clinical samples. However, the significant improvement in resuscitation techniques during the last 30 years has now changed the types of infection caused by *Acinetobacter*. In hot and humid areas, e.g., in tropical countries, *Acinetobacter* infections can be community-acquired, and generally manifest as bacteraemia or pulmonary infections [4]. The circumstances that allow *Acinetobacter* to assume a pathogenic role are not well-understood. As *Acinetobacter* is a relatively low-grade pathogen, the pathogenesis of *Acinetobacter* infections probably involves numerous factors, including virulence determinants, which have yet to be investigated. This review focuses on the clinical impact and pathogenesis of *Acinetobacter* infections, as well as the potential role of some possible virulence factors.

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NOSOCOMIAL INFECTIONS

Morbidity and mortality

The clinical impact of *Acinetobacter* infection in terms of morbidity and mortality has been

discussed widely. These bacteria have already been compared to methicillin-resistant *Staphylococcus aureus* (MRSA), and have even been termed the 'Gram-negative MRSA' [5]. However, although the epidemiological behaviour of *Acinetobacter* is similar to that of MRSA, its impact in terms of morbidity and mortality is probably closer to that of coagulase-negative staphylococci [6]. The incidence of *Acinetobacter* causing bloodstream infection has been estimated to be about ten-fold less than that of *S. aureus* (1.5% vs. 14%) [7]. Nevertheless, several reports have alerted clinicians to the emergence of a potentially difficult and dangerous organism that is responsible for outbreaks of infection and can cause severe problems [8,9]. Published data suggest that the crude or related mortality rate ranges from 20% to 60% [9–15]. There are few studies on attributable mortality using multivariate analysis, although this is the most important type of study. The attributable mortality rate revealed by these few studies is *c.* 10–20% [10,12,14,16].

Within the genus, *Acinetobacter baumannii* appears to be the species of greatest clinical importance, but other species of the '*A. baumannii* complex' (comprising *A. baumannii*, *Acinetobacter calcoaceticus*, and the unnamed sp. 3 and sp. 13 of Tjernberg and Ursing) are also of clinical importance. The *A. baumannii* complex contains isolates that are multiresistant to antibiotics and that have been responsible for many outbreaks of infection throughout the world [17]. The *A. baumannii* complex should be considered to be as different from other *Acinetobacter* spp. as *S. aureus* is from coagulase-negative staphylococci. Other *Acinetobacter* spp. are involved only rarely in human disease and outbreaks of infection, and are generally isolated from patients who are already suffering from severe underlying disease.

Routine clinical diagnostic laboratories often have difficulties in differentiating *A. baumannii* from other *Acinetobacter* spp., as conventional bacteriological tests are insufficient for accurate identification. Nevertheless, it is clear that *A. baumannii* began to spread rapidly among patients in intensive care units (ICUs) in the 1980s. The reported incidence of *A. baumannii* nosocomial infections varied from 3.7% to 8.2% in Spain in 1992 [18], and was 9% in Europe as a whole in 1995 [3].

Nosocomial bloodstream infections

Bacteraemia is currently one of the infections with the highest mortality rate in hospitals. A survey by the Health Protection Agency in England found that patients with *Acinetobacter* bacteraemia were generally aged >50 years, that the majority were male, and that 5% were hospitalised in general wards and 54% in ICUs [7,12,18,19]. Risk-factors have been defined in many studies, and are essentially the same as those identified for other opportunistic bacteria [12,18,19]. One study reported sepsis and/or septic shock in 19% of patients with *Acinetobacter* bacteraemia [20]. This observation highlighted the true pathogenicity of a few strains, with a crude mortality rate of *c.* 42%. An attributable mortality rate of 7.8% found in one survey was related to a delay in the initiation of appropriate therapy [7]. Mixed infections are frequent in cases of *Acinetobacter* bacteraemia, and this observation has opened a debate on the importance of bacterial synergy in cases of bacteraemia [21]. *Acinetobacter* spp. other that *A. baumannii* generally represent 10–15% of *Acinetobacter* isolates from cases of bacteraemia. However, exceptions exist, and Valero *et al.* [20] identified a high rate of non-*A. baumannii* isolates causing bacteraemia among patients in haematology wards, while most *A. baumannii* isolates were from patients in ICUs.

Nosocomial pneumonia

Prior to the 1970s, *Acinetobacter* infections were mostly post-surgical urinary tract infections, and *Acinetobacter* spp. were isolated primarily from patients hospitalised in surgical or medical wards. The significant improvement in resuscitation techniques during the last 30 years has changed the types of infections caused by *Acinetobacter*. Today, the most important role of these bacteria is as a cause of nosocomial pneumonia, particularly following the use of mechanical ventilatory procedures. McDonald *et al.* [22] reported an increase from 0.64% to 6.4% in the incidence of nosocomial pneumonia caused by *Acinetobacter* between 1976 and 1990. Larger surveys have reported a patchy distribution in the prevalence among centres, but with an overall incidence of 8%. *Acinetobacter* spp. were found in 24 of 49 participating hospitals in the Scope surveillance system in the USA [7], while the