Nosocomial and community-acquired Acinetobacter infections

Marie-Laure Joly-Guillou

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Introduction

Members of the genus *Acinetobacter* are involved in a wide spectrum of infections. Although this organism is mainly associated with nosocomial infections, these bacteria have been recently shown involved in community-acquired infection. Over 1,000 published papers refer to "infections by antibiotic resistant *Acinetobacter* in the international literature." This opportunistic commensal bacterium was initially considered a relatively low-grade pathogen and frequently ignored until the 1960s, even when isolated from clinical samples. However, marked improvement in culture techniques in the last 30 years increased awareness of infections due to *Acinetobacter*. Prior to the 1970s, nosocomial infections by this organism were mainly detected after surgical procedures or in the urinary tract from patients hospitalized in intensive care units (ICU), but since the 1980s, acinetobacters were found rapidly spread among ICU patients. At the present time, this bacterium represents about 9–10% of all nosocomial infections, but the majority are due to respiratory tract infection. The origin of such infections is known to be both endogenous and exogenous, and the introduction of single-use disposable patient items is now known to limit endogenous infection. Nevertheless, transmission of the bacteria by the hands of hospital staff is now known to be an important risk factor for patient colonization. Of the many different microbial species isolated from various environments, *Acinetobacter baumannii* is known to be the most frequently involved in human infections. Although the reservoirs outside of hospital environments are not clearly defined, community acquired infection and infection related to war or earthquakes have been recognized and may be due to presence of these microbes in the soil. The severity of such infection by this bacterium depends on the site of infection and the degree of a patient's immune competence related to underlying disease. *Acinetobacter* may cause mild to severe illness and can be fatal. However, a consensus whether this organism is indeed highly pathogenic is not established since this organism is

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thought to be mainly a low-grade pathogen. It is likely that increased pathogenesis by this microbe involves numerous factors, including virulence factors that are not yet clear. However, there is now increased interest in this pathogen the last 30 years (Livermore, 2003), since recognition of antibiotic multiresistant strains, including pan resistance, emerged in an outbreak in a clinical unit (Del Mar et al., 2005; Fierobe et al., 2001; Mah et al., 2001; Rello, 2003; Simor et al., 2002; Smolyakov et al., 2003). In hot and humid areas such as the tropics, *Acinetobacter* infections are usually community acquired, in general bacteremias, or primary infections (Anstey et al., 2002).

Mortality and Morbidity

The clinical impact of *Acinetobacter* infections in terms of morbidity and mortality is highly variable. Since the 1980s, *A. baumannii* has been found to spread rapidly among ICU patients. Recorded incidences of nosocomial infection vary from about 4–8.2 % in Spain in the period 1990–1997 (Vaque et al., 1999) or 9% in 1995 in Europe (Vincent et al., 1995). These bacteria have been compared to *Staphylococcus aureus* resistance to methicillin (MRSA) and even designated "Gram negative MRSA" (Rello, 2003). This epidemiological spread of *Acinetobacter* is similar to MRSA, and has an impact on morbidity and mortality similar to coagulase-negative staphylococci (Rello and Diaz, 2003). However, the incidence of *Acinetobacter* bacteremia is estimated to be ten fold less than *S. aureus* (1.5% as compared to 14%, respectively, Wisplinghoff et al., 2000). Nevertheless, some authors believe clinicians should be alert to the emergence of this potentially difficult and dangerous organism responsible for infectious outbreaks, which may cause severe problems (Kaul et al., 1996; Theaker et al., 2003). Recently published reports concerning overall mortality rates vary from 20 to nearly 60%. However, there have only been a few studies of mortality rates using multivariant analysis. Although this type of study should be further performed, mortality rates in a few studies have been often shown to be between 10% and 20% (Blot et al., 2003; Poutanen et al., 1997; Wisplinghoff et al., 2000). The species *A. baumannii* appears to be of the greatest clinical importance. Nevertheless, there is a close relationship between *A. baumannii* complex species (*A. baumannii*, calcoaceticus sp. 3 and the sp 13 of Tenberg and Ursing). These isolates are more resistant to antibiotics and responsible for numerous outbreaks throughout the world (Bergogne-Bérézin et al., 1996). The *A. baumannii* complex is considered different from other species, similar to differences between *S. aureus* and coagulase-negative staphylococci. Other *Acinetobacter* species are not frequently involved in human infection outbreaks, but are generally isolated from patients suffering from severe underlying disease. Furthermore, clinical laboratories sometimes have difficulties differentiating other *Acinetobacter* species from *A. baumannii*, since conventional tests are usually insufficient for accurate identification.

Nosocomial Bacteremia

Bacteremia caused by *Acinetobacter* is currently one of the infections with highest mortality in hospitals. A survey of the health protection agency in England showed that patients with bacteremia were more than 50 years of age and the majority male. Among these patients, 5% were hospitalized in general wards and 54% in ICUs (Wisplinghoff et al., 2000). Risk factors were defined in many studies and found similar to other opportunistic bacteria (Blot et al., 2003; Vaque et al., 1999; Poutanen et al., 1997). Sepsis and/or septic shock were observed in one study in 19% of bacteremias (Valero et al., 2001). However, this observation stressed the major pathogenicity of only a few strains. Although, the overall mortality rates were about 40%, mortality of about 8% was reported in one survey related to inappropriate therapy (Wisplinghoff et al., 2000). Mixed infections are frequent in *Acinetobacter* bacteremia and this may be related to bacterial synergy. *A. baumannii* infection generally represents about 10–15% of *Acinetobacter* bacteremia isolates. However, in another survey, Valero et al. (2001) identified a high rate of non-*A. baumannii* bacteremia. These species were preferentially isolated from patients hospitalized in hematology wards, rather than the majority of *A. baumannii* isolated from ICU patients.

Nosocomial Pneumoniae

Before the 1970s, *Acinetobacter* infections were mainly detected in postsurgical and urinary/renal disease patients. Since these bacteria were isolated mainly from patients hospitalized in surgical or medical wards, significant improvement in culture techniques the last 30 years provided a fuller view of *Acinetobacter* infection frequency (Fagon et al., 1996; Garnacho et al., 2003). McDonald et al. (1999) reported that from 1976 to 1990, the incidence of nosocomial pneumoniae due to *Acinetobacter* increased from less than 1 to no more than 6%. At the present time, these organisms from ventilator-associated pneumonia are known to be markedly increasing. Infection rates of 30–75% have been reported for nosocomial pulmonary infection due to *Acinetobacter* species, with the highest rates reported in ventilator-dependent patients (Cardenosa Cendrero 1999). The use of specific microscopic and laboratory techniques has demonstrated the increasing role of *A. baumannii* in such nosocomial pneumonia (Chastre et al., 1996), and the distribution as well as the prevalence of these bacteria were observed in a large survey (Rello 1999). Incidence varied from one center to another, with an overall incidence of 8% in the SCOPE virulence system. *Acinetobacter* species were found present in only 24 or 49 USA hospitals participating (Wisplinghoff et al., 2000). From the century surveillance program of 144 Latin American countries, Gales et al. (2002) found *Acinetobacter* species in only 7 countries. The epidemiology of nosocomial

respiratory colonization and/or infection with *A. baumannii* is known to be complex due to co-existence of epidemics with unrelated sporadic cases caused by different strains (Chastre, 2003).

Wound and Burn Infections

A. baumannii is a common cause of nosocomial infection in burn patient populations. Infections caused by these bacteria are less severe than that caused by other organisms. In a recent report, burn patients with *Acinetobacter* infection had more severe burns and co-morbidities. However, on multivariant analysis, infection with *A. baumannii* was not found associated with mortality (Albrecht et al., 2006). Outbreaks due to this organism have been described in burn units and many of the infections have been associated with antibiotic multiresistant strains. A persistent outbreak is often related to persistent contamination of the hospital environment (Simor et al., 2002). In 1985, Sherertz and Sullivan described a persistent outbreak due to contamination of patient mattresses.

Infective Endocarditis

Endocarditis due to *Acinetobacter* is relatively rare, but with high mortality and reported mainly in hospitalized patients with previous heart disease factors (Valero et al., 1999). Rarely reported, acinetobacters also constitute one of several causes of early prosthetic valve endocarditis. A diffuse red bacterial maculopapullar may be encountered (Olut et al., 2005). Some cases of prosthetic vale endocarditis due to *Acinetobacter lwoffi* have also been described (Starakis et al., 2006).

Neonatal Nosocomial Infections

Neonatal sepsis is the major cause of death in newborns despite sophisticated neonatal intensive care. There have been only a few reports of *Acinetobacter* infections or outbreaks in neonates. *A. baumannii* is responsible for the majority of neonatal sepsis (greater than 72 hrs of age) with a mortality rate of 11% compared to early onset sepsis due to group *B streptococcus*. Infections have been described in ventilated infants with a birth weight less than 1500 g and hospitalized for more than 7 days (Mehr et al., 2002; Jiang et al., 2004; Von Dolinger et al., 2005). The intestinal flora of a neonate is considered the reservoir of the organism, and the rate of intestinal carriage of these bacteria is a variable risk factor.

Meningitis

Acinetobacter is a rare cause of meningitidis. Sporadic cases have been reported following neurosurgical procedures (Chen et al., 2005). In 1989, an outbreak of *Acinetobacter meningitis* was described in a group of children with leukemia (Kelkar et al., 1989) following administration of intrathecal methotrexate and due to inappropriately sterilized needles. Three of the children died as a result of meningitis. Risk factors include the presence of a continuous connection between the ventricles and the external environment, a ventriculostomy, a CSF fistula, presence of an indwelling ventricular catheter for more than 5 days, and the use of antimicrobial agent. Metan et al. (2007) in Turkey reported a wide prevalence of multiresistant *Acinetobacter* causing meningitis in neurosurgical patients. The surveillance of local pathogens in neurosurgical wards should guide the selection of empirical therapy and an effective infection control program.

Pathogenesis, Dissemination, and Outbreaks

In clinical practice, *Acinetobacter* infections are closely associated with surgery or artificial devices, and colonization precedes infection. For patients to become infected, various risk factors are necessary for pathogenesis. This is one explanation for the increasing incidence of these infections, especially in ICUs, because of multiple manipulations due to surgical practice. The use of endotracheal tubes, intravascular, ventricular, or urinary catheters often leads to opportunistic bacteria colonizing the site. In this regard, the presence and duration of invasive procedures, as well as exposure to wide-spectrum antibiotics have been identified as risk factors in many studies for acquisition of *Acinetobacter* (Koeleman et al., 2001). Because *Acinetobacter* is transmitted via the hands of the staff, the care workload "omega score" could represent a good marker for determination of these risk factors (Saulnier et al., 2001). Bacterial overgrowth in the stomach is another pathway that may be involved in development of nosocomial pneumonia or bacteremia. This may occur under conditions of diminution of acid secretion often observed in ICU patients. *Acinetobacter* readily multiply under these conditions (Cardenosa et al., 1999). *A. baumannii* is responsible for occasional but sudden outbreaks, which are usually unexpected and then difficult to control. The local circumstances of clinical units and the environment determine the type of infection, dissemination, and risk of outbreak. *Acinetobacter*, considered a low-grade pathogen, can remain on or in an individual without causing illness. Dissemination via the hand of the staff often remains unnoticed or undetected (Wang et al., 2003). Infections are less numerous than by another pathogen such as *S. aureus*. In a clinical unit, the ratio of colonized to infected patients may be as high as 2 to 1 for methicillin-resistant *S. aureus* vs.10 to 1 for *Acinetobacter*. Patients with

infection manifestations are likely to be the "tip of the iceberg" and dissemination is likely to be the "underground of a mushroom bed" (Bayuga et al., 2002). When infections due to *Acinetobacter* emerge, the number of colonized patients is probably already high and the alert to prevent an outbreak given too late (Carbonne et al., 2005). During an outbreak, all environment surfaces can be a reservoir. *Acinetobacter* readily survive, especially in ICUs, and this can be the case from days to weeks even in dry conditions. Under such conditions, even health care workers may be colonized on various sites with *Acinetobacter* (Wagenvort et al., 2002).

Wartime and Earthquake Infections

Acinetobacter has been found responsible for infections in various particular situations. After the Marmara earthquake in Northwest Turkey in 1999, 220 of 630 victims were hospitalized and 18.6% had nosocomial infections. Among these, 31.2% of the isolates were *A. baumannii* and two were pan-resistant strains. The prevalence of *Acinetobacter* infections before the earthquake was of 7.3% in the same hospital ICU without identification of multiresistant strains (Oncül et al., 2002). The literature from the Vietnam, Iran-Iraq, and Gulf wars identified multidrug resistant *Acinetobacter* as a war-zone community acquired pathogen, both colonizing and infecting casualties (Mitchell et al., 2007; Tong, 1972). Early infections observed in soldiers were more often soft tissue or surgical wound infections. Osteomyelitis caused by *Acinetobacter* occurred, but less frequently reported (Davis et al., 2005). During January 1, 2002—August 31, 2004, military health officials identified 102 patients by blood culture that grew *A. baumannii* in medical facilities treating service members injured in Afghanistan and the Iraq/Kuwait region. The number of patients with *Acinetobacter* blood infections in 2003 and 2004 exceeded those reported in previous years. These findings suggest environmental contamination of wounds as a potential source (CDC, 2004).

Community-acquired Infections

More than 100 cases of community-acquired pneumonia have been described since the 1980s. Meningitis, cellulitis, or primary bacteremia have been noticed rarely. Acute pneumonia is the most frequent community-acquired infection. Patients with acute pneumonia generally have a history of alcohol abuse, diabetes, cancer, or broncho-pulmonary disease. The literature often described a fulminating course of infection and septic shock in about 30% of cases, as well as respiratory failure. Patients frequently have productive sputum and hemoptysis. The high mortality rate has been related to the patient background and delay in appropriate therapy. In a recent study, Leung et al. (2006) found that

32% of patients with pneumonia have bacteraemia. Generally, bacteremia has been described mainly in tropical developing countries such as New Guinea, Thailand, or even Australia (Anstey et al., 2002; Wang et al., 2002). A few cases occur in temperate countries such as Spain, France, or the United States (Megarbane et al., 2000; Salas et al., 2003). Cases are more prevalent in warm and humid months, even in temperate regions (McDonald et al., 1999). Increasing colonization may probably be linked to perspiration and overuse of broad-spectrum antibiotics in a population. A few studies have shown the presence of *Acinetobacter* in body lice, fleas, or ticks and propose their role as vectors in transmission of community-acquired infections, particularly among the homeless (La Scola et al., 2001).

Pathogenicity and Virulence

In the past, *Acinetobacter* was considered an organism with low virulence. The occurrence of fulminating community-acquired *Acinetobacter* pneumonia indicates that this bacterium can be also highly pathogenic and cause invasive disease. Studies on virulence factors are still at an elementary stage. Nonspecific adherence factors such as fimbriae have been described in *Acinetobacter* (Bergogne-Bérézin et al., 1996; Rathinavelu et al., 2003). Under iron-deficient conditions, bacterial growth can be accompanied by production of receptors and iron-regulated catechol siderophores, which favor bacterial growth and expression of virulence factors (Goel and Kapil, 2001). *Acinetobacter* lipopolysacharide, similar to those of other Gram-negative bacilli, is responsible for lethal toxicity in mice and the positivity of the amebocyte-lysate test (endotoxin detection) during *Acinetobacter* septicemia. This lipopolysacharide is involved in resistance to complement in human serum and acts in synergy with the capsular exopolysaccharide.

Complement appears to play a role in the bactericidal activity of human serum. A relationship between the degree of resistance of Gram-negative bacteria isolated from bacteremic patients to the lytic activity of complement in vitro and their ability to penetrate into human fluids has been described. Lipopolysaccharide and capsular polysaccharide are both involved in this phenomenon. Capsular polysaccharide is known to block complement access to the microbial cell wall and prevent the triggering of the alternate pathway of complement activation, demonstrated in experimental models of Gram-negative infections. Exopolysaccharide production by pathogenic bacteria is a major virulence factor and thought to protect bacteria from host defenses and lethal for mice and cytotoxic for phagocytic cells. About 30% of strains produce exopolysaccharide. This production has been studied in *A. calcoaceticus* BD4, a strain that synthesizes a thick exopolysaccharide capsule composed of rhamnose, mannose, glucose, and glucuronic acid. In experimental studies, exopolysaccharide-producing strains of *A. calcoaceticus* were shown to be more

pathogenic than nonproducing strains, especially in polymicrobial infections with other species of higher virulence (Obana, 1986). Quorum sensing is a widespread regulatory mechanism among Gram-negative bacteria like *Pseudomonas aeruginosa*. Four different quorum-sensing signal molecules capable of activating N-acylhomoserine-lactone biosensors have been found in *Acinetobacter* clinical strains, with maximal activity reached at the stationary growth phase (Gonzalez et al., 2001). Quorum-sensing might be a central mechanism for auto-induction of multiple virulence factors in an opportunistic pathogen like *Acinetobacter* and should be studied for clinical implications.

Conclusion and Perspectives

Many parameters, such as host factors, bacterial burden, and strain virulence, may have important roles in promoting clinical infection in colonized patients. *Acinetobacter* is often multiresistant to antibiotics and thus, identifying factors influencing virulence would permit identifying low-virulent strains against which antibiotic therapy could be avoided. In contrast, identification of highly virulent colonizing strains in the respiratory tract could lead to greater prophylactic use of antibiotic treatment of high-risk patients. Careful hand washing with soap and water, as well as alcohol-based hand sanitizers, should be vigorously encouraged.

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