**Acinetobacter baumannii**

An emerging opportunistic pathogen

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**Introduction**

*Acinetobacter baumannii* is an opportunistic bacterial pathogen primarily associated with hospital-acquired infections. The recent increase in incidence, largely associated with infected combat troops returning from conflict zones, coupled with a dramatic increase in the incidence of multidrug-resistant (MDR) strains, has significantly raised the profile of this emerging opportunistic pathogen. Herein, we provide an overview of the pathogen, discuss some of the major factors that have led to its clinical prominence and outline some of the novel therapeutic strategies currently in development.

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This phenomenon of multidrug-resistant (MDR) pathogens has increasingly become a cause for serious concern with regard to both nosocomial and community-acquired infections. In particular, high incidences of MDR bacteremia (bloodstream infections) have been noted among US Army service members following Operation Iraqi Freedom (OIF). Interest from the scientific community over the past 15 years has led to significant advances of our understanding of this organism. 

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**Genus Acinetobacter**

The Dutch microbiologist Beijerinck first isolated the organism in 1911 from soil using minimal media enriched with calcium acetate. Originally described as *Micrococcus calco-aceticus*, the genus Acinetobacter (coming from the Greek “akineto,” meaning non-motile) was proposed some 43 years later by Brisou and Prevot to differentiate it from the motile organisms within the genus Achromobacter. The genus Acinetobacter was widely accepted by 1968 after Baumann et al. published a comprehensive study of organisms such as *Micrococcus calco-aceticus, Alcaligenes hemolytans, Mima polymorpha, Moraxella luoffii, Herellea vaginicola and Bacterium anitratum*, which concluded that they belonged to a single genus and could not be further sub-classified into different species based on phenotypical characteristics. In 1971, the sub-committee on the Taxonomy of Moraxella and Allied Bacteria officially acknowledged the genus Acinetobacter based on the results of Baumann’s 1968 publication.

The genus Acinetobacter, as currently defined, comprises Gram-negative, strictly aerobic, non-fermenting, non-fastidious, non-motile, catalase-positive, oxidase-negative bacteria with a DNA G+C content of 39% to 47%. Following DNA-DNA hybridization studies performed by Bouvet and Grimont in 1986, the Acinetobacter genus now consists of 26 named species and nine genomic species. Four species of Acinetobacters (*A. calcoaceticus, A. baumannii*, Acinetobacter genomic species 3 and Acinetobacter genomic species 13TU) have such phenotypic similarities that they are difficult to differentiate, and as such are often referred to as the *A. calcoaceticus*-complex. This nomenclature can be misleading as the environmental species *A. calcoaceticus* has not been implicated in clinical disease, while the other three species in the *A. calcoaceticus*-complex are perhaps the most clinically significant species, being implicated in both community-acquired and nosocomial infections.
Species

Acinetobacters may be identified presumptively to the genus level as Gram-negative, catalase-positive, oxidase-negative, non-motile, non-fermenting coccobacilli. However, the organisms are often difficult to de-stain and, as such, are often incorrectly identified as Gram-positive (see Fig. 1). There is no definitive metabolic test that can distinguish Acinetobacters from other non-fermenting Gram-negative bacteria. A method which is often used to identify to the genus level relies on the ability of the mutant A. baylyi strain BD413 trpE27 to be transformed by crude DNA of any Acinetobacter species to a wild-type phenotype (i.e., the transformation assay of Juni17). While for species level identification, the 28 available phenotypic tests have proven to be 95.6% effective in identifying human skin-derived Acinetobacters.18 However, phenotypic tests alone have proven to be ineffective in identifying more recently discovered genomic strains of Acinetobacters.5

More advanced molecular diagnostic methods have been developed for identification of Acinetobacters to the species level, these include:

- Amplified 16S rRNA gene restriction analysis (ARDRA)19
- High-resolution fingerprint analysis by amplified fragment length polymorphism (AFLP)20
- Ribotyping21
- tRNA spacer fingerprinting22
- Restriction analysis of the 16S–23S rRNA intergenic spacer sequences23
- Sequence analysis of the 16S–23S rRNA gene spacer region24
- Sequencing of the rpoB (RNA polymerase β-subunit) gene and its flanking spacers25

Natural Habitat

Organisms belonging to the genus Acinetobacter are often considered to be ubiquitous in nature given that they can be recovered from almost all soil and surface water samples.13 This understanding has contributed to the common misconception that A. baumannii is also ubiquitous.26 While not all Acinetobacters find their habitat in the natural environment, a thorough and systematic study to investigate the natural occurrence of the various Acinetobacter species in the environment has yet to be performed.5

As a pathogen, A. baumannii specifically targets moist tissues such as mucous membranes or areas of the skin that are exposed, either through accident or injury. Skin and soft tissues infected with A. baumannii initially present with a “peau d’orange” appearance (similar to the skin of an orange) followed by a sandpaper-like presentation which eventually gives way to clear vesicles on the skin.3 In areas of skin disruption hemorrhagic bullae can be seen, with a visible necrotizing process followed by bacteremia.3 If left untreated, this infection can lead to septicemia and death. Although it is likely that A. baumannii is responsible for these recognizable features, copathogens, such as Klebsiella pneumoniae, Candida albicans and Enterococcus faecalis, are thought to be a contributing factor. These co-pathogens may cause necrotizing infection and may create a nidus of entry into the bloodstream for A. baumannii.3

Despite its association with skin infections, A. baumannii is found only rarely as part of the normal skin microflora, with one study estimating that only 3% (at most) of the population are colonized by the bacterium.18 Interestingly, Acinetobacter was recovered from 22% of body lice sampled from homeless people, suggesting another potentially important reservoir for the pathogen.25

A key risk group for A. baumannii infection is members of the armed forces who have been deployed to conflict zones, particularly Iraq, earning A. baumannii the notorious moniker of ‘Iraqibacter.’ The dry, sandy conditions associated with these desert campaigns provide an ideal environment for the physiologically robust A. baumannii, making it the main source of infection among injured soldiers.9 A 2003 study on board the US Navy
The ability of A. baumannii to form biofilms allows it to grow persistently in unfavorable conditions and environments. Indeed, A. baumannii has been shown to form biofilms on abiotic surfaces, which can include glass and equipment used in intensive care units, and/or on biotic surfaces such as epithelial cells. When pili attach to abiotic surfaces, they initiate the formation of microcolonies, followed by the full development of biofilm structures. BAP are present on the surface of bacterial cells and they contribute to biofilm development and maturation by stabilizing the mature biofilm on abiotic or biotic surfaces. Environmental signals, such as metal cations, also play a role in controlling the formation of biofilms, increasing the ability of A. baumannii to adhere to particular surfaces.

Other key proteins that have been shown to contribute to A. baumannii virulence include phospholipase D and C. While phospholipase D is important for resistance to human serum, epithelial cell evasion and pathogenesis, phospholipase C enhances toxicity to epithelial cells. Along with OmpA, fimbra, also expressed on the surface of the bacterial cell, contribute to the adhesion of the pathogen to host epithelia.

### Antibiotic Resistance

The rapid emergence of multi- and pandrug-resistant strains of Acinetobacter highlights the organism’s ability to quickly acclimatize to selective changes in environmental pressures. The upregulation of the organism’s innate resistance mechanisms coupled with the acquisition of foreign determinants have played a crucial role in the express route the organism has taken to becoming a multidrug-resistant pathogen.

A 2006 study undertaken by Fournier et al. compared the genome of AYE and SDF Acinetobacter using whole shotgun genome sequences. In France, the epidemic AYE strain had a 26% mortality rate in infected patients, while the SDF strain came from the same geographical region, but was associated with human body lice, and was fully susceptible to antimicrobial agents. The genomic comparisons revealed that the genome of the virulent AYE strain contained an 86 kb region called a resistance island that contained a cluster of 45 resistance genes. The homologous location in the susceptible strain exhibited a 20 kb genomic island that is devoid of these resistance markers. This ability to “switch” its genomic structure goes some way to explaining the speed with which Acinetobacter captures resistance markers when under antibacterial pressure, such as may occur in a high risk environment, such as in hospital intensive care units (where broad spectrum antimicrobials are commonly used). Sequence similarity and phylogenetic analyses confirmed that most of the resistance genes found in the Acinetobacter strain AYE had been recently acquired from bacteria of the genera Pseudomonas, Salmonella or Escherichia.

All genomic variants of A. baumannii contain a non-inducible chromosomal AmpC cephalosporinase, also known as Acinetobacter-derived cephalosporinases (ADCs). The presence of an upstream IS element known as ISAba1 determines the regulation of the AmpC gene. Overexpression of AmpC cephalosporinase and resistance to extended spectrum cephalosporin is intrinsically linked to the presence of ISAba1. Cefepime and carbapenems, however, appear to be stable in response to these enzymes.

A. baumannii also possess an intrinsic class D oxacillinase belonging to the OXA-51-like group of enzymes that constitutes...
over 40 sequence variants. The ubiquitous nature of OXA-51-like genes in *A. baumannii* has led to this gene becoming an important genetic marker in identification of the organism to the species level. OXA-51-like enzymes are able to hydrolyze penicillins (benzylpenicillin, ampicillin, ticarcillin and piperacillin) and carbapenems (imipenem and meropenem) but do so only very weakly. A significant contribution to lactam resistance by OXA-51-like enzymes therefore requires the presence of an insertion element ISAba1 upstream of the gene, which acts as a strong transcriptional promoter. The most common enzymatic mode of carbapenem resistance is the production of oxacillinases encoded by genes of the blaOXA-23, blaOXA-40 and blaOXA-58-like lineage.

In Europe, the spread of multidrug-resistant *Acinetobacter* is not confined to hospitals within a city but also occurs on a national scale, mostly through inter-hospital patient transfers, for example the spread of the so-called Southeast clone and the Oxa-23 clones 1 and 2 in southeast England. International transfer of colonized patients has led to the introduction and subsequent epidemic spread of multidrug-resistant *A. baumannii* strains from southern into northern European countries, such as Belgium and Germany.

In an industry-supported surveillance report (MYSTIC) from 48 European hospitals for the period 2002–2004, just 73.1% of *A. baumannii* isolates were susceptible to meropenem and 69.8% were susceptible to imipenem. Susceptibility to other antibiotics was also very low, with 32.4%, 34.0% and 47.6% being susceptible to cefazidime, ciprofloxacin and gentamicin, respectively.

There is a long history of multidrug-resistant *A. baumannii* infections occurring in the United States. In 1991 and 1992, outbreaks of carbapenem-resistant *A. baumannii* were observed in a hospital in New York City. This followed an outbreak of infections due to ESBL-producing *Klebsiella pneumoniae* during which use of imipenem increased substantially. In a more recent industry-supported surveillance study including isolates of *Acinetobacter* collected between 2004 and 2005 from 76 centers throughout the United States, only 60.2% were susceptible to imipenem.

Numerous outbreaks of pandrug-resistant *A. baumannii* have been documented in Asian and Middle Eastern hospitals. Rates of non-susceptibility in SENTRY (Anti-microbial Surveillance Program) isolates (2001–2004) exceeded 25% for imipenem and meropenem, 40% for cefepime and cefazidime, 40% for ampicillin-sulbactam, 35% for amikacin, and 45% for ciprofloxacin. It is worth noting that resistance to tigecycline and polymyxin B (drugs relied on heavily to treat infection with *A. baumannii*) both already exist in this region.

**Clinical Symptoms**

*A. baumannii* infections are implicated across a wide range of anatomical regions and with varying severity and patient outcomes. There is considerable debate relating to the actual clinical impact of infection and its relationship to patient mortality. While a number of studies have concluded that infection with *Acinetobacter* has a detrimental effect on patient outcome, other similar studies implied little or no effect on patient outcome as a result of infection.

The lack of consensus is most likely due to the difference in the approaches of the various studies; some being prospective while others have been of retrospective samples. The results generated by some studies have also only identified the organism to genus level but not to species level, with many referring to infection with *Acinetobacter calcoaceticus-baumannii* complex which could conceivably indicate colonization with the environmental species *Acinetobacter calcoaceticus* coupled with a polymicrobial infection, rather than a monomicrobial infection with a virulent *Acinetobacter* species such as MDR *Acinetobacter*.

**Hospital-acquired pneumonia.** Ventilator associated pneumonia (VAP) is commonly linked to infection. Longer periods of hospitalization, longer time on mechanical ventilation and prior use of antibiotics are the recognized factors increasing the risk of VAP due to *Acinetobacter*. Nosocomial outbreaks have also been described due to health care professionals with colonized hands and poor personal hygiene; such individuals may act as opportunist carriers of an epidemic stain. Contaminated ventilators or respiratory care equipment as well as intra-hospital transmission may also contribute to the beginning of an outbreak.

**Community-acquired pneumonia.** Pneumonia acquired outside of the hospital setting and caused by *Acinetobacter* has been noted in Australia and Asia. The source of infection may be throat carriage, which occurs in up to 10% of community residents with excessive alcohol consumption. It is characterized by a severe and sudden onset coupled with secondary bloodstream infection and has a mortality rate of between 40% and 60%.

**Bloodstream infections.** In a seven year review (1995–2002) of nosocomial bloodstream infections in the United States, *Acinetobacter* accounted for 1.3% of all monomicrobial bloodstream infections. *Acinetobacter* was a more common cause of ICU-acquired bloodstream infection than of non-ICU-ward infection (1.6% vs. 0.9% of bloodstream infections, respectively, in those locations). Crude mortality figures overall from *Acinetobacter* bloodstream infection was 34.0% to 43.4% in the ICU and 16.3% outside the ICU. *Acinetobacter* bloodstream infection had the third highest crude mortality rate in the ICU, exceeded only by *P. aeruginosa* and *Candida* spp infections. It is notable that 102 patients had bloodstream infections at sites treating US military personnel injured in Iraq or Afghanistan from January 1, 2002 and August 31, 2004.

**Battlefield trauma and other wounds.** *Acinetobacter* is a well-documented pathogen of burns units and is difficult to treat in patients with severe burns. However, infection of the skin and soft tissue outside of a military environment is uncommon. A retrospective review of 57 patients with SSTI revealed that eight cases were infected with *Acinetobacter*. In this instance all patients were male, ranging in age from 13 to 55 and of both American and Iraqi nationality. The median time from trauma to diagnosis with *Acinetobacter* infection was 15 d. All eight patients had a similar clinical presentation of SSTI; characteristic cellulitis with “peau d’orange” appearance, severe infection resulted in formation of bullae on the skin surface. The mortality rate in this instance was 12.5% (i.e., one of the eight died; however given that the patient was admitted with a gunshot wound to the groin, mortality cannot be solely assigned to infection).
Meningitis. Nosocomial, post-neurosurgical Acinetobacter meningitis is becoming increasingly more common with many other Gram-negative bacteria also becoming problematic in post-operative care. Installation of an external ventricular drain becomes a site for opportunistic infection. The mortality rate may be as high as 70%; however it is not possible to discern the definitive cause of mortality.

**Therapeutic Strategies**

Existing antimicrobials. As mentioned previously, one of the distinguishing features of A. baumannii is its impressive array of acquired antibiotic resistance mechanisms, which although beyond the scope of this review, includes degradation enzymes against β-lactams, modification enzymes against aminoglycosides, altered binding sites for quinolones, and a variety of efflux mechanisms and changes in outer membrane proteins (see Peleg et al. for a detailed overview). Any and all of these elements can be combined to result in a highly drug-resistant pathogen; making selection of an appropriate empirical antimicrobial agent extremely difficult. Indeed, given the probability that A. baumannii would be most likely resistant to one of the common first line antibiotics, treatment of the infection should be performed following sound consideration of antimicrobial susceptibility testing. Nevertheless, as a delay in accessing correct treatment may have adverse consequences for a patient’s health, carbapenems such as Imipenem are often given as a drug of preference for serious and suspected Acinetobacter infections. However, despite its utility short-term, this prescription method jeopardizes future efficacy of such drugs as effective antimicrobial agents.

Future therapies. Given the rapid and extensive development of antibiotic resistance, several attempts have been made to develop alternative control strategies for dealing with A. baumannii including, but not limited to the following:

**Bacteriophage.** Recently renewed interest in the area of antibacterial phage therapy has gained some traction. Due to the high specificity of phage and their ability to work quickly, bacteriophage therapy is being re-examined as an alternative treatment to help counteract the phenomenon of antibiotic resistance. Indeed, a recent study by Yang et al. has resulted in the isolation and characterization of the virulent AB1 bacteriophage which has been shown to be effective against A. baumannii and as such represents a novel therapeutic of some potential.

**Bactericidal gene transfer therapy.** The design and delivery of vectors containing bactericidal genes that can be introduced into recipient pathogenic organisms by conjugation using attenuated donor cells is referred to as bactericidal gene transfer therapy. While the therapeutic potential of this approach is limited by the requirement for donor cells to be in contact with the pathogen (to facilitate vector transfer), positive effects have nonetheless been observed using murine burn infection models. Using this approach, Shankar et al. have shown that mice treated with a single dose of 10^9 CFU of donor cells containing bactericidal genes had lower levels of A. baumannii in burn wounds compared with untreated mice.

**Cathelicidins.** Marsupials give birth to immunologically naïve, altricial young that reside in the maternal pouch for 9–10 mo while being supported by a sophisticated lactation system. In the pouch, cathelicidins interact with and destroy Gram-positive and Gram-negative bacteria, protozoa and fungi via electrostatic interactions between their positively charged peptides and the negatively charged molecules found in the cell membranes of their targets. The best studied cathelicidin is human LL-37; the only human cathelicidin, it exhibits both anti-tumor and anti-HIV activity. The Tammar Wallaby cathelicidin WAM1 has been shown to be effective against Acinetobacter, and is 3–80 times more potent than LL-37 against a host of bacterial pathogens. WAM1 was not hemolytic against human red blood cells indicating potential for parenteral use in humans. Indeed, WAM1’s anti-microbial activity and tolerance to salt concentrations similar to those found in the human body make it seem a likely candidate for further in vivo studies.

**Radioimmunotherapy.** Although not yet not exploited as a therapeutic antimicrobial strategy in the clinic, radioimmunotherapy can target microorganisms as quickly and efficiently as cancer cells. This approach takes advantage of the specificity of antigen-antibody interactions to deliver radionuclides that emenate lethal doses of cytotoxic radiation directly to the target cell. Producing only transient hematological toxicity in experimental animals, radioimmunotherapy has been successfully adapted for the treatment of bacterial, fungal and viral infections. Given that previous studies have already described the development of antibodies against A. baumannii, the application of radioimmunotherapy as a novel therapeutic strategy for A. baumannii is a definite possibility.

**Photodynamic therapy.** Involves the combination of nontoxic photosensitizers (PSs) with oxygen and visible to produce reactive oxygen species that oxidize biomolecules thereby killing cells. The use of photodynamic therapy (PDT) to treat localized bacterial infections generally involves the topical application of a PS into the infected tissue, followed by illumination with red (or near-infrared) which is capable of penetrating the infected tissue. Using a murine burn wound model, this technique has previously been shown to be effective against A. baumannii while having no obvious effects on wound healing. Recently, Tsai et al. investigated the effect of chitosan, a polycationic biopolymer, on increasing the efficacy of PDT against a number of pathogens including A. baumannii. Under conditions in which hematoporphyrin-PDT exhibited a bactericidal effect on a 2- to 4-log scale, subsequent treatment with chitosan (0.025%) for a further 30 min completely eradicated the bacteria (at a starting inoculum of 10^6 CFU/ml). Chitosan alone did not exert significant antimicrobial activity, without prior PDT, suggesting that the potentiated effect of chitosan worked only after the bacterial damage induced by PDT. Furthermore, the potentiated PDT effect of chitosan appears to be related to the level of PDT damage and the deacetylation level of the chitosan.

**Nanoparticle technology.** Nitric oxide (NO) has been shown to exhibit potent antimicrobial activity as well as playing an important role in modulating immunity and regulating wound healing. Using nanotechnology based on a silane hydrogel,
Friedman et al.\(^{84}\) have designed a stable nitric oxide (NO)-releasing nanoparticle (NO-np) platform. With the potential to serve as a novel, inexpensive and easily applied topical class of antimicrobials, this technology has been shown to be effective for the treatment of complex cutaneous infections such as those caused by \textit{A. baumannii}. Indeed, Mihu et al.\(^{85}\) recently demonstrated the effect of NO-np against \textit{A. baumannii} using murine wound and soft tissue models. Compared with control animals, NO-np-treated mice exhibited significant reductions in bacterial burden, enhanced wound healing rates and less collagen degradation by bacterial collagenases.

### Conclusions

In conclusion, \textit{A. baumannii} is an important opportunistic and emerging pathogen that can lead to serious nosocomial infections. Its pathogenic potential includes the ability to adhere to surfaces, form biofilms, display antimicrobial resistance and acquire genetic material from unrelated genera, making it a versatile and difficult therapeutic practice.\(^{86}\) The optimal treatment for \textit{A. baumannii}, especially nosocomial infections resulting from multiple resistant strains, remains to be established. It is thus a clinical imperative that well-designed procedures are put in place to help guide clinicians on decisions regarding the current best therapeutic practice.\(^{87}\) Furthermore, new experimental approaches are warranted to develop and evaluate novel therapeutic strategies for dealing with \textit{A. baumannii} infections.

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