An increasing threat in hospitals: multidrug-resistant *Acinetobacter baumannii*

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Abstract | Since the 1970s, the spread of multidrug-resistant (MDR) *Acinetobacter* strains among critically ill, hospitalized patients, and subsequent epidemics, have become an increasing cause of concern. Reports of community-acquired *Acinetobacter* infections have also increased over the past decade. A recent manifestation of MDR *Acinetobacter* that has attracted public attention is its association with infections in severely injured soldiers. Here, we present an overview of the current knowledge of the genus *Acinetobacter*, with the emphasis on the clinically most important species, *Acinetobacter baumannii*.

DNA–DNA hybridization

Determines the degree of similarity between the genomic DNA of two bacterial strains; the gold standard to assess whether organisms belong to the same species.

Pandrug-resistant

In this Review, refers to *A. baumannii* that are resistant to all available systemic anti-*A. baumannii* antimicrobial agents, except for polymyxins.

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Intensive care units (ICUs) of hospitals harbour critically ill patients who are extremely vulnerable to infections. These units, and their patients, provide a niche for opportunistic microorganisms that are generally harmless for healthy individuals but that are often highly resistant to antibiotics and can spread epidemically among patients. Infections by such organisms are difficult to treat and can lead to an increase in morbidity and mortality. Furthermore, their eradication from the hospital environment can require targeted measures, such as the isolation of patients and temporary closure or even reconstruction of wards. The presence of these organisms, therefore, poses both a medical and an organizational burden to health-care facilities.

One important group of bacteria that is associated with these problems is the heterogeneous group of organisms that belong to the genus *Acinetobacter*. This genus has a complex taxonomic history. Since the 1980s, in parallel with the emergence of acinetobacters as nosocomial pathogens, the taxonomy of the genus has been refined; 17 named species have been recognized and 15 genomic species (gen.sp.) have been delineated by DNA–DNA hybridization, but these do not yet have valid names (TABLE 1). The species that is most commonly involved in hospital infection is *Acinetobacter baumannii*, which causes a wide range of infections, including pneumonia and blood-stream infections. Numerous studies have reported the occurrence of multidrug-resistant (MDR) *A. baumannii* in hospitals, and at some locations pandrug-resistant strains have been identified. Currently, *A. baumannii* ranks among the most important

nosocomial pathogens. Additionally, the number of reports of community-acquired *A. baumannii* infection has been steadily increasing, although overall this type of infection remains rare. Despite the numerous publications that have commented on the epidemic spread of *A. baumannii*, little is known about the mechanisms that have favoured the evolution of this organism to multidrug resistance and epidemicity. In this Review, we discuss the current state of knowledge of the epidemiology, antimicrobial resistance and clinical significance of acinetobacters, with an emphasis on *A. baumannii*. The reader is also referred to previous reviews of this organism that have been written by pioneers in the field^{1,2}.

Identification of *Acinetobacter* species

In 1986, a phenotypic system for the identification of *Acinetobacter* species was described³, which together with a subsequent simplified version⁴ has proven useful for the identification of most, but not all, *Acinetobacter* species. In particular, *Acinetobacter calcoaceticus*, *A. baumannii*, gen.sp. 3 and gen.sp. 13TU cannot be separated well by this system⁴. These species are also highly similar by DNA–DNA hybridization⁵ and it has therefore been proposed that they should be grouped together into the so-called *A. calcoaceticus*–*A. baumannii* (Acb) complex⁴. From a clinical perspective this might not be appropriate, as the complex combines three of the most clinically relevant species (*A. baumannii*, gen.sp. 3 and gen.sp. 13TU) with an environmental species (*A. calcoaceticus*). It is noteworthy that the performance of commercial systems for species identification that are used in diagnostic microbiology is also unsatisfactory.

Using these systems, the clinically relevant species of the Acb complex are frequently uniformly identified as *A. baumannii* and many other species are not identified^{6–8}. These problems have led to the development of genotypic methods for *Acinetobacter* species identification, some of which are discussed in BOX 1 (also see FIG. 1). Currently, precise species identification is not feasible in most laboratories, except for a few *Acinetobacter* reference laboratories. In light of the difficulties in distinguishing *A. baumannii*, gen.sp. 3 and gen.sp. 13TU, in this Review these species will be referred to as *A. baumannii* (in a broad sense) unless otherwise stated.

Epidemiology of clinical acinetobacters

The natural habitat of *Acinetobacter* species. Most *Acinetobacter* species have been found in clinical specimens (TABLE 1), but not all are considered to be clinically significant. One important question is where does *A. baumannii* come from? Furthermore, are there environmental or community reservoirs? As mentioned earlier, *A. baumannii*, gen.sp. 3 and gen.sp. 13TU are the most frequent species that are found in human clinical specimens^{5,9,10}. Of these, gen.sp. 3 was the most prevalent species among clinical isolates in a Swedish study⁵. In 2 European studies, *Acinetobacter lwoffii* was the most

Table 1 | **Classification of the genus *Acinetobacter***

Species	Source	References
Species that have valid names		
<i>Acinetobacter calcoaceticus</i>	Soil and humans (including clinical specimens)	3,5
<i>Acinetobacter baumannii</i>	Humans (including clinical specimens), soil, meat and vegetables	3,5,17
<i>Acinetobacter haemolyticus</i>	Humans (including clinical specimens)	3,5
<i>Acinetobacter junii</i>	Humans (including clinical specimens)	3,5
<i>Acinetobacter johnsonii</i>	Humans (including clinical specimens) and animals	3,5
<i>Acinetobacter lwoffii</i> (including gen.sp. 9)	Humans (including clinical specimens) and animals	3,5
<i>Acinetobacter radioresistens</i>	Humans (including clinical specimens), soil and cotton	3,5,105
<i>Acinetobacter ursingii</i>	Humans (including clinical specimens)	39
<i>Acinetobacter schindleri</i>	Humans (including clinical specimens)	39
<i>Acinetobacter parvus</i>	Humans (including clinical specimens) and animals	40
<i>Acinetobacter baylyi</i>	Activated sludge and soil	100,106
<i>Acinetobacter bouvetii</i>	Activated sludge	106
<i>Acinetobacter towneri</i>	Activated sludge	106
<i>Acinetobacter tandoii</i>	Activated sludge	106
<i>Acinetobacter grimontii</i>	Activated sludge	106
<i>Acinetobacter tjernbergiae</i>	Activated sludge	106
<i>Acinetobacter gerneri</i>	Activated sludge	106
Species that have provisional designations		
<i>Acinetobacter venetianus</i>	Sea water	107
Gen.sp. 3	Humans (including clinical specimens), soil and vegetables	3,5,17
Gen.sp. 6	Humans (including clinical specimens)	3,5
Gen.sp. 10	Humans (including clinical specimens), soil and vegetables	3,5,17
Gen.sp. 11	Humans (including clinical specimens) and animals	3,5
Gen.sp. 13BJ or 14TU*	Humans (including clinical specimens)	5,108
Gen.sp. 14BJ	Humans (including clinical specimens)	108
Gen.sp. 15BJ	Humans (including clinical specimens)	108
Gen.sp. 16	Humans (including clinical specimens) and vegetables	17,108
Gen.sp. 17	Humans (including clinical specimens) and soil	17,108
Gen.sp. 13TU	Humans (including clinical specimens)	5
Gen.sp. 15TU	Humans (including clinical specimens)	5
Gen.sp. 'between 1 and 3'	Humans (clinical specimens)	9
Gen.sp. 'close to 13TU'	Humans (clinical specimens)	9

*Identical designations have been given independently to three genomic species (gen.sp.) in two reports^{5,108}; it is common practice to label these species by the initials of their respective authors, Tjernberg and Ursing (TU)⁵ or Bouvet and Jeanjean (BJ)¹⁰⁸.

Isolate

A population of bacterial cells in pure culture that is derived from a single colony.

Box 1 | Genotypic methods for *Acinetobacter* species identification

The genotypic identification of *Acinetobacter* species can be achieved by whole-genome fingerprinting, restriction analysis of a particular DNA sequence and DNA-sequence determination. For identification of a strain, the genotype that is obtained by one of these methods is compared with a library of reference strains. Only a few of the many described methods have been validated by the use of large numbers of strains from all described species. Here, we discuss three methods: amplified fragment length polymorphism (AFLP), amplified 16S ribosomal DNA (rDNA) restriction analysis (ARDRA) (both AFLP and ARDRA are well validated) and DNA-sequence analysis.

AFLP (see figure, part a) comprises the following steps: digestion of cellular DNA with two restriction enzymes (a frequent and a rare cutter); ligation of adaptors to the restriction fragments; selective amplification of the fragments; electrophoresis of fragments on a sequencing machine; and visualization of the restriction profiles³⁹. The profiles are compared by cluster analysis to those of a reference library of AFLP fingerprints using dedicated software. This method is not only useful for species identification³⁹ (FIG. 1), but also for the identification of strains (typing)³² and clones³⁶. Although AFLP is robust within a laboratory, the results cannot be compared between laboratories.

ARDRA (see figure, part b) comprises amplification of 16S rDNA sequences, followed by restriction of the amplified fragments with five restriction enzymes and electrophoresis⁹⁹. The resulting profiles are compared with a library of restriction profiles. ARDRA restriction patterns can be compared between laboratories.

DNA-sequence analysis, of the 16S rDNA sequence in particular, is a widely used approach to assess relationships between microorganisms, and the data is universally comparable. However, some unrelated *Acinetobacter* species have high 16S rDNA sequence similarities, even though some closely related species are found in different branches of the 16S rDNA phylogenetic tree¹⁰⁰. Further studies are needed to assess the intra- and interspecies similarity-cut-off levels. Another promising gene for species identification is *rpoB*¹⁰¹.

predominant species to be found on the skin of healthy individuals, with carrier rates of 29% and 58%, whereas other *Acinetobacter* species, including *Acinetobacter junii*, *Acinetobacter johnsonii*, *Acinetobacter radioresistens* and gen.sp. 15BJ, were detected at lower frequencies^{11,12}. The carrier rates for *A. baumannii* (including gen.sp. 13TU) in these studies ranged from 0.5 to 3%, whereas for gen.sp. 3 the rates ranged from 2 to 6%^{11,12}. The faecal carriage of *A. baumannii* among non-hospitalized individuals in the United Kingdom and the Netherlands was 0.9%¹³. The most predominant species in faecal samples from the Netherlands were *A. johnsonii* (17.5%) and gen.sp. 11 (4%)¹³. *A. baumannii* was also recovered from the body

lice of homeless people¹⁴ and it was proposed that the organisms were associated with transient bacteraemia in these individuals. In a study in Hong Kong, the carrier rates of *A. baumannii*, gen.sp. 3 and gen.sp. 13TU on the skin of healthy individuals were 4, 32 and 14%, respectively¹⁵. Thus, the carrier rates for gen.sp. 3 and gen.sp. 13TU in that study were strikingly higher than in the European studies. These findings indicate that, at least in Europe, the carriage of *A. baumannii* in the community is relatively low. Apart from its occurrence in humans, *A. baumannii* has also been associated with infection and epidemic spread in animals at a veterinary clinic¹⁶.

Figure 1 | Amplified fragment length polymorphism (AFLP) analysis of *Acinetobacter* strains. A condensed dendrogram of the AFLP (described in BOX 1) fingerprints of 267 *Acinetobacter* reference strains of 32 described genomic species. All species are well separated at the 50% cluster-cut-off level, which emphasizes the power of this method for the delineation and identification of *Acinetobacter* species.

There are few available data on the environmental occurrence of *A. baumannii*, gen.sp. 3 and gen.sp. 13TU, but these species have been found in varying percentages in vegetables, fish, meat and soil^{17,18}. *A. baumannii* has also recently been found in aquacultures of fish and shrimp farms in Southeast Asia¹⁹. However, it is not yet clear to what extent these findings are attributable to an environmental niche or to contact with humans or animals.

A. baumannii has been described as a soil organism, but without the support of appropriate references²⁰. It was probably assumed that the wide occurrence of unspiciated acinetobacters in soil and water²¹ is also applicable to *A. baumannii*. However, in fact, there is little evidence that *A. baumannii* is a typical soil

resident. Taken together, the existing data indicate that *A. baumannii* has a low prevalence in the community and that its occurrence in the environment is rare.

***A. baumannii* in hospitals.** The most striking manifestation of *A. baumannii* is the endemic and epidemic occurrence of MDR strains in hospitals. The closely related gen.sp. 3 and gen.sp. 13TU might have a similar role^{22–24}, and their involvement could have been underestimated as these species are phenotypically difficult to discriminate from *A. baumannii*. Most investigations of *A. baumannii* in hospitals have been *ad hoc* studies that were triggered by an outbreak. More in-depth studies of the prevalence of this species in hospitals, including antibiotic-resistant and antibiotic-susceptible strains, are required to better understand its true importance.

Depending on the local circumstances, and the strain in question, the pattern of an outbreak can vary. There can be a common source or multiple sources and some strains have a greater tendency for epidemic spread than others. Epidemiological typing — mostly by genotypic methods, such as amplified fragment length polymorphism (AFLP) analysis (BOX 1) — is an important tool that can distinguish an outbreak strain from other, concurrent strains, and assess the sources and mode of transmission of the outbreak strain.

A scheme that depicts the dynamics of epidemic *A. baumannii* on a hospital ward is provided in FIG. 2. An epidemic strain is most commonly introduced by a patient who is colonized. Once on a ward, the strain can then spread to other patients and their environment. *A. baumannii* can survive in dry conditions²⁵ and during outbreaks has been recovered from various sites in the patients' environment, including bed curtains, furniture and hospital equipment²⁶. These observations, and the success that cleaning and disinfecting patients' rooms has had in halting outbreaks, emphasize the role of the hospital environment as a reservoir for *A. baumannii* during outbreaks. The bacteria can be spread through the air over short distances in water droplets and in scales of skin from patients who are colonized²⁷, but the most common mode of transmission is from the hands of hospital staff. Patients who are colonized or infected by a particular *A. baumannii* strain can carry this strain at different body sites for periods of days to weeks²⁸, and colonization can go unnoticed if the epidemic strain is not detected in clinical specimens^{2,29}.

Population studies of *A. baumannii*. Comparative typing of epidemic strains from different hospitals has indicated that there can be spread between hospitals. For example, during a period of outbreaks in the Netherlands that involved eight hospitals, one common strain was found in three of these hospitals and another common strain was found in two others²⁶. Similar observations of interhospital spread of MDR strains in particular geographical areas have been made in the Czech Republic³⁰, the United Kingdom³¹, Portugal³² and the United States³³.

Highly similar, but distinguishable, strains have been found at different locations and at different time points,

Endemic

The constant presence of an infectious agent in a given geographical area or hospital.

Figure 2 | Overview of the dynamics between patients, bacteria and the hospital environment. The possible modes of *Acinetobacter baumannii* entry into a ward are shown. Entrance through a colonized patient is the most likely mode. However, introduction by healthy carriers is also conceivable, although it is not known whether the rare strains that circulate in the community have epidemic potential. Once on a ward, *A. baumannii* can spread from the colonized patient to the environment and other susceptible patients. The direct environment of the patient can become contaminated by excreta, air droplets and scales of skin. Interestingly, *A. baumannii* can survive well in the dry environment²⁵, a feature it shares with staphylococci. Hence, the contaminated environment can become a reservoir from which the organism can spread. The acquisition of *A. baumannii* by susceptible patients can occur through various routes, of which the hands of hospital staff are thought to be the most common, although the precise mode of transmission is usually difficult to assess.

Clones

A group of bacteria that were isolated independently from different sources in time and space, but share so many identical traits that it is likely that they evolved from a common ancestor.

Typing method

A tool that differentiates bacterial strains below the species level.

Ribotyping

A typing method in which chromosomal DNA is digested by restriction enzymes, fragments are separated by electrophoresis and, finally, particular fragments are detected by labelled rRNA probes to generate DNA-banding patterns, which allows the differentiation of bacterial isolates.

without a direct epidemiological link. It is assumed that these strains represent particular lineages of descent (clones). Examples are European clones I–III^{34–36}, which have been delineated by a range of genotypic typing methods, such as AFLP analysis (BOX 1a; FIG. 1), ribotyping, macrorestriction analysis by pulsed-field gel electrophoresis and, most recently, multilocus sequence typing (see both MLST systems in Further information). Strains that belong to these clones are usually highly resistant to antibiotics, although within a clone there can be variation in antibiotic susceptibility. Apparently, these clones are genetically stable strains that are particularly

successful in the hospital environment and evolve slowly during their spread. Whether these strains have particular virulence attributes or an enhanced ability to colonize particular patients (discussed below) remains to be established. Their wide spread might be explained by the transfer of patients between hospitals and regions over the course of time, although in many cases there is no evidence for this. It is also possible that they circulate at low rates in the community and are able to expand in hospitals under selective pressure from antibiotics. So far, their resistance to antimicrobial agents is the only known selectively advantageous trait.

Clinical impact of *Acinetobacter* infections

Nosocomial infections. *Acinetobacter* are opportunistic pathogens that have been implicated in various infections that mainly affect critically ill patients in ICUs. Hospital-acquired *Acinetobacter* spp. infections include: ventilator-associated pneumonia; skin and soft-tissue infections; wound infections; urinary-tract infections; secondary meningitis; and bloodstream infections. These infections are mainly attributed to *A. baumannii*, although gen.sp. 3 and gen.sp. 13TU have also been implicated. Nosocomial infections that are caused by other *Acinetobacter* species, such as *A. johnsonii*, *A. junii*, *A. lwoffii*, *Acinetobacter parvus*, *A. radioresistens*, *Acinetobacter schindleri* and *Acinetobacter ursingii*, are rare and are mainly restricted to catheter-related bloodstream infections^{8,37–40}. These infections cause minimal mortality and their clinical course is usually benign, although life-threatening sepsis has been observed occasionally⁴¹. The rare outbreaks of some of these species (for example, *A. junii*) have been found to be related to contaminated infusion fluids⁴¹.

The risk factors that predispose individuals to the acquisition of, and infection with, *A. baumannii* are similar to those that have been identified for other MDR organisms. These include: host factors such as major surgery, major trauma (in particular, burn trauma) and prematurity in newborns; exposure-related factors such as a previous stay in an ICU, the length of stay in a hospital or ICU, residence in a unit in which *A. baumannii* is endemic and exposure to contaminated medical equipment; and factors that are related to medical treatment such as mechanical ventilation, the presence of indwelling devices (such as intravascular catheters, urinary catheters and drainage tubes), the number of invasive procedures that are performed and previous antimicrobial therapy⁴². Risk factors that are specific for a particular setting have also been identified, such as the hydrotherapy that is used to treat burn patients and the pulsatile lavage treatment that is used for wound débridement^{43,44}.

The most frequent clinical manifestations of nosocomial *A. baumannii* infection are ventilator-associated pneumonia and bloodstream infection, both of which are associated with considerable morbidity and mortality, which can be as high as 52%^{45,46}. Risk factors for a fatal outcome are severity-of-illness markers, an ultimately fatal underlying disease and septic shock at the onset of infection. Bacteraemic *A. baumannii* pneumonia has a particularly poor prognosis⁴⁶. A characteristic clinical manifestation is cerebrospinal-shunt-related meningitis, caused by *A. baumannii* in patients who have had neurosurgery⁴⁷. Wound infections have been reported mainly in patients who have severe burns or trauma, for example, soldiers who have been injured during military operations^{43,48}. Urinary-tract infections related to indwelling urinary-tract catheters usually run a more benign clinical course and are more frequent in rehabilitation centres than in ICUs⁴⁹.

The clinical impact of nosocomial *A. baumannii* infection has been a matter of continuing debate. Many studies report high overall mortality rates in patients that have *A. baumannii* bacteraemia or pneumonia^{45,46}. However, *A. baumannii* mainly affects patients with severe underlying disease and a poor prognosis. It has therefore been argued that the mortality that is observed in patients with *A. baumannii* infections is caused by their underlying disease, rather than as a consequence of *A. baumannii* infection. In a case-control study, Blot and colleagues⁵⁰ addressed whether *A. baumannii* contributes independently to mortality and concluded that *A. baumannii* bacteraemia is not associated with a significant increase in attributable mortality. Similar findings for *A. baumannii* pneumonia have been reported by Garnacho and colleagues⁵¹. By contrast, in recent reviews of matched cohort and case-control studies, Falagas and colleagues^{52,53} concluded that *A. baumannii* infection was associated with an increase in attributable mortality, ranging from 7.8 to 23%. These contradictory conclusions show that the debate on the clinical impact of *A. baumannii* is still ongoing.

Community-acquired infections. *A. baumannii* is increasingly recognized as an uncommon but important cause of community-acquired pneumonia. Most of the reported cases have been associated with underlying conditions, such as alcoholism, smoking, chronic obstructive pulmonary disease and diabetes mellitus. Community-acquired *A. baumannii* pneumonia appears to be a unique clinical entity that has a high incidence of bacteraemia, a fulminant clinical course and a high mortality that ranges from 40 to 64%. It has been observed almost exclusively in tropical climates, in particular in Southeast Asia and tropical Australia^{54,55}. It is currently unclear, however, if host factors or particular virulence factors are responsible for these severe infections. Multidrug resistance in these organisms is uncommon⁵⁵. Other manifestations of community-acquired *A. baumannii* infections are rare.

Infections associated with natural disasters and war casualties. A characteristic manifestation of nosocomial *A. baumannii* is wound infection that is associated with natural or man-made disasters, such as the Marmara earthquake that occurred in 1999 in Turkey, the 2002 Bali bombing and military operations^{48,56,57}. A strikingly high number of deep-wound infections, burn-wound infections and osteomyelitis cases have been reported to be associated with repatriated casualties of the Iraq conflict⁴⁸. Isolates often had multidrug resistance. Based on the common misconception that *A. baumannii* is ubiquitous, it has been argued that the organism might have been inoculated at the time of injury, either from previously colonized skin or from contaminated soil. However, recent data clearly indicate that contamination of the environment of field hospitals and infection transmission in health-care facilities have had a major role in the acquisition of *A. baumannii*⁵⁸.

Macrorestriction analysis

A typing method in which chromosomal DNA is digested with rare-cutting enzymes, so creating large fragments that are separated in an alternating electric field (pulsed-field electrophoresis) according to their size.

Osteomyelitis

An infection of bone or bone marrow.

Figure 3 | The factors that contribute to *Acinetobacter baumannii* environmental persistence and host infection and colonization. Adherence to host cells, as demonstrated in an *in vitro* model using bronchial epithelial cells⁶², is considered to be a first step in the colonization process. Survival and growth on host skin and mucosal surfaces require that the organisms can resist antibiotics and inhibitory agents and the conditions that are exerted by these surfaces. Outgrowth on mucosal surfaces and medical devices, such as intravascular catheters and endotracheal tubes⁶¹, can result in biofilm formation, which enhances the risk of infection of the bloodstream and airways. Quorum sensing⁵⁹ might have a regulatory role in biofilm formation. Experimental studies have identified various factors that could have a role in *A. baumannii* infection, for example, lipopolysaccharide has been shown to elicit a proinflammatory response in animal models^{67,68}. Furthermore, the *A. baumannii* outer membrane protein A has been demonstrated to cause cell death *in vitro*⁶⁴. Iron-acquisition mechanisms⁶⁵ and resistance to the bactericidal activity of human serum⁶⁶ are considered to be important for survival in the blood during bloodstream infections. Environmental survival and growth require attributes such as resistance to desiccation^{25,60}, versatility in growth requirements³, biofilm-forming capacity⁶¹ and, probably, quorum-sensing activity⁵⁹. Finally, adequate stress-response mechanisms are thought to be required for adaptation to different conditions.

Quorum sensing

The phenomenon whereby the accumulation of signalling molecules enables a single cell to sense the number of bacteria (cell density) that are present, which allows bacteria to coordinate certain behaviours or actions.

Epidemicity and pathogenicity

The fact that colonization with *A. baumannii* is more common than infection, even in susceptible patients, emphasizes that the pathogenicity of this species is generally low. However, once an infection develops, it can be severe. Studies on the epidemicity and pathogenicity factors of *A. baumannii* are still at an elementary stage. A number of putative mechanisms that might have a role

in colonization, infection and epidemic spread are summarized in FIG. 3. Genetic, molecular and experimental studies are required to elucidate these mechanisms in more detail.

Recent DNA sequencing of a single *A. baumannii* strain identified 16 genomic islands that carry putative virulence genes that are associated with, for example, cell-envelope biogenesis, antibiotic resistance, autoinducer production, pilus biogenesis and lipid metabolism⁵⁹. Resistance to desiccation, disinfectants^{25,60} and antibiotics is important for environmental survival. The extraordinary metabolic versatility³ of *A. baumannii* could contribute to its proliferation on a ward and in patients. Pilus-mediated biofilm formation on glass and plastics has been demonstrated⁶¹. If formed on medical devices, such as endotracheal tubes or intravascular catheters, these biofilms would probably provide a niche for the bacteria, from which they might colonize patients and give rise to respiratory-tract or bloodstream infections. Electron microscopy studies have demonstrated that pili on the surface of acinetobacters interact with human epithelial cells⁶². In addition, thread-like connections between these bacteria were suggestive of an early phase of biofilm formation. The pili and hydrophobic sugars in the O-side-chain moiety of lipopolysaccharide (LPS)⁶³ might promote adherence to host cells as a first step in the colonization of patients. Quorum sensing, the presence of which has been inferred from the detection of a gene that is involved in autoinducer production⁵⁹, could control the various metabolic processes, including biofilm formation.

Resistance to antibiotics, as well as the protective conditions of the skin (such as dryness, low pH, the resident normal flora and toxic lipids) and those of the mucous membranes (such as the presence of mucus, lactoferrin and lactoperoxidase and the sloughing of cells) are prerequisites for bacterial survival in a host that is receiving antibiotics. *In vitro* and animal experiments have identified various factors that could have a role in *A. baumannii* infection. For example, *A. baumannii* outer membrane protein A (*AbOmpA*, previously called Omp38) has been associated with the induction of cytotoxicity⁶⁴. Iron-acquisition mechanisms⁶⁵ and serum resistance⁶⁶ are attributes that enable the organism to survive in the bloodstream. The LPS and lipid A of one strain, at the time named *A. calcoaceticus*, had biological activities in animals that were similar to those of other enterobacteria⁶⁷. These included lethal toxicity, pyrogenicity and mitogenicity for mouse-spleen B cells. More recently, *A. baumannii* LPS was found to be the major immunostimulatory component that leads to a proinflammatory response during *A. baumannii* pneumonia⁶⁸ in a mouse model.

Taken together, the chain of events from environmental presence to the colonization and infection of patients demonstrates the extraordinary ability of *A. baumannii* to adapt to variable conditions. This ability suggests that the organism must possess, in addition to other factors, effective stress-response mechanisms. Together with its resistance to antibiotics, these mechanisms might explain the success of particular *A. baumannii* strains in hospitals.

Antimicrobial susceptibility and treatment

Antimicrobial resistance. *A. baumannii* is attracting much attention owing to the increase in antimicrobial resistance and occurrence of strains that are resistant to virtually all available drugs⁶⁹. This organism is generally intrinsically resistant to a number of commonly used antibiotics, including aminopenicillins, first- and second-generation cephalosporins and chloramphenicol^{70,71}. It also has a remarkable capacity to acquire mechanisms that confer resistance to broad-spectrum β -lactams, aminoglycosides, fluoroquinolones and tetracyclines¹. Numerous studies have suggested an upward trend in strains of *A. baumannii* that are resistant to these agents. However, because of the scarcity of large-scale surveillance studies from the 1970s to the 1990s and the difficulties in comparing local reports, such trends are difficult to quantify on a global level. Resistance rates can vary according to the country and the individual hospital, and depend on biological, epidemiological or methodical factors. For example, local susceptibility testing without correction for predominant MDR epidemic strains tends to overestimate the level of resistance⁷². It has also been shown that MDR isolates from geographically distant areas can be clonally related, whereas susceptible strains are genotypically heterogeneous^{30,34}, which suggests that the problem of resistance might be associated with a limited number of successful *A. baumannii* lineages.

Despite the difficulties that are associated with estimating resistance trends, the potential of *A. baumannii* to develop resistance against virtually all available drugs is unquestionable (TABLE 2). Of particular concern is resistance to carbapenems — broad-spectrum β -lactams that were introduced by 1985 and that, for years, have been the most important agents for the treatment of infections caused by MDR *A. baumannii*. Although clinical *A. baumannii* isolates were shown to be invariably susceptible to these drugs in early studies^{70,71}, hospital outbreaks caused by carbapenem-resistant strains had already been reported by the early 1990s⁷³ and, currently, the frequency of these strains in some areas can exceed 25%⁷⁴. Recently, resistance to polymyxins⁷⁵ and tigecycline⁷⁶ has also been described, which indicates that *A. baumannii* can cause infections that are fully refractory to the currently available antimicrobial armoury.

Resistance mechanisms. The resistance of *A. baumannii* to antimicrobial agents is mediated by all of the major resistance mechanisms that are known to occur in bacteria, including modification of target sites, enzymatic inactivation, active efflux and decreased influx of drugs (TABLE 2). β -lactamases are the most diverse group of enzymes that are associated with resistance, and more than 50 different enzymes, or their allelic forms, have been identified so far in *A. baumannii*. Aminoglycoside resistance has been attributed to at least nine distinct modifying enzymes, which can be found in different combinations in some strains^{77,78}. Specific point mutations in the genes that encode DNA gyrase and topoisomerase IV have been correlated with resistance to fluoroquinolones⁷⁹, and resistance to tetracyclines has been associated with genes that encode tetracycline-specific

efflux pumps⁸⁰. Most genes that encode inactivating enzymes and specific efflux pumps are present only in some strains and are associated with genetic elements such as transposons, integrons or plasmids, which suggests they were acquired by horizontal transfer. Some of these genes are also common in other bacterial genera, whereas others are predominantly associated with the genus *Acinetobacter* (for example, the APH(3')-VI gene) or even with *A. baumannii* (for a list of genes that encode the OXA-type carbapenemases, see TABLE 2).

A few chromosomal resistance genes are present in most, if not all, *A. baumannii* strains. They are normally expressed at a low level but can be overexpressed as a result of genetic events. Chromosomal ADC-type β -lactamases can be upregulated as a consequence of the upstream insertion of an *ISAbal* sequence, which provides an efficient promoter⁸¹. This insertion sequence is widespread in *A. baumannii* and is thought to serve as a 'moving switch' to turn on those genes with which it is juxtaposed⁸². *ISAbal* is also thought to have a key role in some carbapenem-resistant strains by enhancing the expression of the intrinsic OXA-51-like carbapenemases⁸³. Another chromosomal system that is typical of *A. baumannii* is the AdeABC efflux system⁸⁴. Fully susceptible strains that contain the genes that encode AdeABC can spontaneously produce resistance mutations in the *adeS* or *adeR* genes, which regulate AdeABC expression⁸⁵. Upregulation of AdeABC is so far the only mechanism that has been proven to decrease susceptibility to multiple antimicrobial classes in *A. baumannii* (TABLE 2).

The diversity of the determinants that confer resistance of *A. baumannii* to a particular group of antibiotics can best be illustrated by the mechanisms that are associated with carbapenem resistance⁸⁶ (TABLE 2). These include metallo- β -lactamases (VIM-, IMP- and SIM-types), which have been reported worldwide and confer resistance to all β -lactams with the exception of monobactams. Nevertheless, the most widespread carbapenemases in *A. baumannii* are class D β -lactamases. In addition to the intrinsic OXA-51-like enzymes, three unrelated groups of these carbapenem-hydrolysing oxacillinases have been distinguished, which are represented by OXA-23, -24 and -58, respectively. Reduced susceptibility to carbapenems has also been associated with the modification of penicillin-binding proteins and porins or with upregulation of the AdeABC efflux system, and it has been suggested that the interplay of different mechanisms might result in high-level carbapenem resistance in *A. baumannii*⁸⁷.

Despite the progress in the elucidation of the function and genetic basis of particular resistance mechanisms, knowledge of the genetic factors that contribute to multidrug resistance in *A. baumannii* is limited. Although resistance to multiple drugs can be associated with some epidemic lineages^{34,35}, closely related MDR strains can differ greatly from each other in terms of the presence of particular resistance determinants and their combinations⁸⁸. An important observation has recently been made by Fournier and colleagues²⁰, who

Table 2 | **Antimicrobial resistance mechanisms in *Acinetobacter baumannii***

Mechanism or responsible structure	Typical target drug	Note	References
<i>β-lactam hydrolysis</i>			
ADC-1, -3, -4, -6, -7	Cephalosporins	Chromosomal class C (AmpC) βLs. Intrinsic to <i>A. baumannii</i>	109
TEM-1, -2	Aminopenicillins	Narrow-spectrum class A βL	70,110
CARB-5*	Carboxypenicillins	Narrow-spectrum class A βL	111
SCO-1	Penicillins	Narrow-spectrum class A βL. Plasmid encoded	112
TEM-92, SHV-12, PER-1, VEB-1	β-lactams, such as extended-spectrum cephalosporins	Extended-spectrum class A βLs. Plasmid or chromosomal genes flanked by insertion sequences	69
CTX-M-2	Cefotaxime	Extended-spectrum class A βLs. Plasmid encoded	69
OXA-21, -37	Oxacillins	Class D βLs. Class 1 integron-associated genes	113,114
OXA-51-like [‡]	Carbapenems	Chromosomal class D βLs. Intrinsic to <i>A. baumannii</i>	86
OXA-23-like [‡]	Carbapenems	Class D βLs. Plasmid-encoded	86
OXA-24-like [‡]	Carbapenems	Class D βLs. Chromosomally encoded. Found in some epidemic strains	86
OXA-58	Carbapenems	Class D βL. Transposon-borne gene on plasmids or chromosome	86
IMP-1, -2, -4, -5, -6, -11	Carbapenems	Class B metallo-βLs. Class 1 integron-associated genes	86
VIM-2, SIM-1	Carbapenems	Class B metallo-βLs. Class 1 integron-associated genes	86
<i>Aminoglycoside modification</i>			
AAC(3)-Ia	Gentamicin	Acetyltransferase. Class 1 integron-associated gene	77,110
AAC(3)-IIa	Gentamicin, tobramycin	Acetyltransferase	77
AAC(6')-Ib	Tobramycin, amikacin	Acetyltransferase. Class 1 integron-associated gene	77
AAC(6')-Ih, AAC(6')-Iad	Tobramycin, amikacin	Acetyltransferase. Plasmid-encoded	69,115
APH(3')-Ia	Kanamycin	Narrow-spectrum phosphotransferase	77,110
APH(3')-VI	Amikacin, kanamycin	Phosphotransferase. Mostly plasmid encoded	116
ANT(2'')-Ia	Gentamicin, tobramycin	Nucleotidyltransferase. Gene can be associated with class 1 integron	77
ANT(3'')-Ia	Streptomycin	Nucleotidyltransferase. Class 1 integron-associated gene	77,110
<i>Chloramphenicol modification</i>			
CAT1	Chloramphenicol	Acetyltransferase. Plasmid or chromosomally encoded	1
<i>Target alteration</i>			
GyrA	Quinolones	Gyrase subunit. Mostly mutations in the Ser83 codon	79
ParC	Quinolones	Topoisomerase IV subunit. Mostly mutations in the Ser80 codon	79
ArmA	Aminoglycosides	16 ribosomal RNA methylase. Plasmid encoded	117
<i>Active efflux</i>			
AdeABC	Broad (for example, aminoglycosides and quinolones)	Chromosomally encoded RND-type pump. Present in most <i>A. baumannii</i> strains	84,85
AbeM	Broad (for example, quinolones) [§]	Chromosomally encoded MATE-type pump	118
Tet(A)	Tetracycline	Found in most European clone I strains. Transposon borne	80
Tet(B)	Minocycline, tetracycline	Found in most European clone II strains	80
<i>Changes in outer-membrane proteins (OMPs)</i>			
CarO	Carbapenems	29-kDa OMP implicated in drug influx	86
33 to 36-kDa OMP	Carbapenems	Other OMPs (OprD-like protein or 22-kDa OMP) have also been associated with carbapenem resistance	86

The mechanisms listed have been studied in some detail in strains that have been identified as *A. baumannii*. Although some mechanisms are common in this species, others can be rare (for example, SCO-1 and SIM-1). In addition, the following resistance genes have been reported to occur in *A. baumannii*, although their contribution to the resistance phenotype in this species remain to be elucidated: *bla_{pse-1}* (β-lactamase PSE-1); *bla_{OXA-10}* (β-lactamase OXA-10); *bla_{TEM-116}*, *bla_{SHV-2}* and *bla_{SHV-5}* (extended-spectrum β-lactamases TEM-116, SHV-2 and SHV-5, respectively); *cmlA* (chloramphenicol efflux pump); *strA* and *strB* (phosphotransferases APH(3'') and APH(6), respectively); *dhfrI* and *dhfrX* (dihydrofolate reductases); *sulI* (dihydropteroate synthase); *tet(M)* (tetracycline ribosomal protection protein); and *arr-2* (rifampicin ADP-ribosylating transferase). The genetic location of some resistance genes is based on a single observation and may not be their general property. Furthermore, genes that are associated with transposable elements may occur in different replicons. **Acinetobacter* strain not identified to the species level. [‡]Several allelic variants known. [§]As indicated by the expression of *abeM* cloned into *Escherichia coli*. βL, β-lactamase.

Box 2 | Prevention and control of MDR *A. baumannii* in hospitals

There is general agreement that every case of infection or colonization with multidrug-resistant (MDR) *Acinetobacter baumannii* should prompt enforcement of infection-control measures to prevent transmission. The containment strategies for *A. baumannii* are also largely applicable to those for methicillin-resistant *Staphylococcus aureus*, which shows similar epidemiological behaviour. Infection control practices differ between countries. In the Netherlands, strict guidelines have been issued to prevent the transmission of highly resistant microorganisms such as MDR *A. baumannii* (WIP; see Further information). These imply there should be strict isolation of each patient who is infected by MDR *A. baumannii*, even in the absence of an outbreak. A typical example of the various measures that were taken to successfully combat an outbreak that occurred in a medical intensive care unit (ICU) at Leiden University Medical Center, the Netherlands¹⁰², is shown in the figure. The bars indicate the number of new cases per week (patients who were colonized or infected with *A. baumannii*). Outbreak strains (marked in red) were identified by molecular typing and distinguished from sporadic strains (marked in white and grey).

Outbreak management requires an active infection-control programme for patients and hospital personnel, including contact isolation to interrupt transmission as well as active surveillance cultures to detect *A. baumannii*-colonized patients²⁶. Environmental surveillance cultures can identify contaminated surfaces in the patients' environments that might serve as secondary sources for *A. baumannii* transmission or a common source, such as a contaminated ventilator. Molecular typing of *Acinetobacter* isolates recovered from patients and environmental specimens is necessary to establish the magnitude of an outbreak and the possible modes of transmission. Combating large-scale outbreaks in the absence of a common source might require intensified measures, such as improved hand hygiene, cleaning and disinfection of the environment, cohort nursing, the isolation of patients in single rooms, the restriction of access to the ICU, appropriate antibiotic use, improving staffing ratios and, ultimately, closing a ward for cleaning and disinfection^{26,103}. The eradication of an epidemic organism such as MDR *A. baumannii* from a ward is a burden to the hospital, both economically and logistically.

Strict isolation

Rigorous separation to prevent highly contagious or virulent agents that can spread both by air and contact.

Contact isolation

The separation of colonized or infected individuals from others to prevent, or limit, the direct or indirect transmission of diseases that are spread primarily by close or direct contact.

compared the complete genomes of MDR (AYE) and susceptible (SDF) strains of *A. baumannii*. Whereas the AYE strain contained an 86-kilobase (kb) genomic region, termed a resistance island (the largest identified in bacteria to date), in which 45 putative resistance genes were clustered, SDF exhibited a 20-kb genomic island at the homologous location that comprised genes that encode transposases but no resistance genes. A region that is highly similar to the 20-kb island has also been found in the genome of an *A. baumannii* strain that was isolated in 1951 (REF. 59). It is conceivable that such a genomic structure could serve as a 'hot spot'

that facilitates the horizontal acquisition of resistance genes²⁰ and has had a crucial role in the development of *A. baumannii* multidrug resistance.

Options for treatment. Unfortunately, prospective controlled clinical trials for the treatment of *A. baumannii* infections have never been performed. Our knowledge of the best treatment options is therefore based on retrospective analysis of observational studies, small case series and *in vitro* data. Neither broad-spectrum penicillins nor cephalosporins are considered to be effective for the treatment of serious *A. baumannii* infections. Even if isolates are considered to be susceptible according to *in vitro* tests, their minimum inhibitory concentration values are usually close to the clinical breakpoint. Fluoroquinolones have remained active against sporadic *A. baumannii* strains but resistance is now widespread among epidemic *A. baumannii* strains, rendering these antimicrobial drugs no longer useful. Aminoglycosides, in particular tobramycin and amikacin, often retain their activity against resistant *A. baumannii* isolates; however, these compounds are rarely used alone and are more often applied in combination with other antimicrobials.

As *A. baumannii* is becoming increasingly resistant to carbapenems in hospitals worldwide, only a few treatment options remain. Sulbactam, a β -lactamase inhibitor that has unusual intrinsic activity against acinetobacters, has been used successfully for the treatment of MDR *A. baumannii* infections, such as meningitis, ventilator-associated pneumonia and catheter-related bacteraemia^{89,90}. In most patients, sulbactam has been used in combination with ampicillin, but its usefulness is now also increasingly compromised by resistance.

In recent years, there has been a resurgence of the use of polymyxins for the treatment of MDR Gram-negative bacteria, in particular *Pseudomonas aeruginosa* and *A. baumannii*. An increasing body of evidence suggests that intravenous polymyxins can be used successfully for the treatment of ventilator-associated *A. baumannii* pneumonia, with less nephrotoxicity observed than had been anticipated⁹¹. Alternatively, these drugs can be applied topically by the use of an aerosol⁹². Resistance of *A. baumannii* against polymyxins is still extremely rare⁷⁵. Success rates of up to 60% have been reported, but the true efficacy of these antimicrobials remains to be shown in prospective studies.

Tigecycline was the first glycylcycline antibiotic to be launched and is one of the few new antimicrobials that has activity against Gram-negative bacteria that encompass not only most Enterobacteriaceae but also — at least *in vitro* — MDR *A. baumannii*. Several studies have tested the *in vitro* activity of tigecycline against *A. baumannii* and reported good bacteriostatic activity against strains that have a wild-type susceptibility profile, as well as those that are resistant to imipenem⁷². However, current evidence casts doubt on the role of tigecycline as a treatment for MDR *A. baumannii* infection, with reports of high tigecycline resistance⁹³ and the occurrence of an *A. baumannii* bloodstream infection in a patient who received tigecycline⁷⁶.

Minimum inhibitory concentration

The lowest concentration of an antibiotic that inhibits visible growth of the organism.

Clinical breakpoint

A discriminatory antimicrobial concentration that is used to interpret the results of susceptibility testing and to define bacterial populations as susceptible, intermediate or resistant based on the likelihood of therapeutic success.

Antimicrobial combination therapy appears to be a reasonable alternative for the combat of MDR *A. baumannii*. A considerable number of *in vitro* studies, and animal studies using a mouse model of pneumonia, have been carried out to analyse the effect of combination therapy^{94–97}. Suggested combinations include imipenem and amikacin; colistin and rifampin; and imipenem, rifampin and colistin. Clinical experience with combination therapy is limited. In the light of the few agents that are currently available to treat MDR *A. baumannii* infections, alternative treatment strategies and agents are urgently needed. A recent study has shown that, in an animal model, the lactoferrin-derived peptide hLF(1–11) is a promising candidate for the treatment of MDR *A. baumannii*⁹⁸. However, new antimicrobials that have activity against *A. baumannii* are not expected to be available within the next decade.

Conclusion and challenges

Since the 1980s, the taxonomy of the genus *Acinetobacter* has undergone extensive changes, with the recognition of more than 30 gen.sp. The biological significance of most species other than those of the Acb complex remains to be elucidated owing to a lack of practical identification methods. This situation is expected to improve, however, in the near future with the introduction of well-validated sequence-based identification methods.

The occurrence of MDR and pandrug-resistant *A. baumannii* is a growing source of concern, and the exploration of new antibiotics, including host-defence peptides, is urgently required. Apart from MDR strains, there are many antibiotic-susceptible strains of *A. baumannii*, but their prevalence in hospitals and the community is unknown. It is a challenge to assess whether these strains have the potential to emerge to multidrug resistance (and epidemicity) once they enter an antibiotic-rich niche, such as a hospital. Basic questions remain to be answered about the role of the upregulation of resistance genes that

are already present in the genome and the contribution of acquired resistance genes, including the possibility that they are stably integrated into the chromosome. It is also possible that the MDR strains that circulate in hospitals are distinct lineages or groups of lineages within *A. baumannii*, as has already been shown for strains that belong to European clones I–III. The recently developed MLST systems (see both MLST systems in Further information) are important tools that can be used to investigate the prevalence of particular strains at a global scale. However, these systems are based on the similarity of housekeeping genes and the genes that confer resistance and virulence could be located on mobile elements and clustered in genomic islands that are not linked to particular sequence types. Multi-strain genome analysis will probably provide some insight into these questions.

Little is known about the bacterial mechanisms that explain the success of *A. baumannii* in the hospital environment. Genomics, proteomics and fitness studies are expected to be helpful approaches to clarify the remarkable adaptability of the bacteria to variable conditions and selective pressures. Furthermore, apart from general host or treatment factors, there might be intrinsic host factors, such as a particular genetic constitution or innate immune status, that make a specific host susceptible to colonization and infection. Progress is also expected in this area.

The eradication of epidemic *A. baumannii* from the hospital environment demands a great effort (BOX 2). Some countries have managed to keep the microorganism at a sporadic level, with outbreaks occurring only occasionally. In many other countries, however, the organisms are endemic or epidemic. The combat of MDR *A. baumannii* (and other MDR organisms) reaches far beyond the hospital level and requires a combined strategy of decision makers and health-care officials, the challenge being to make hospitals a safer place for patients who are critically ill.

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DATABASES

Entrez Genome Project: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=genomeprj>
Acinetobacter baumannii | *Pseudomonas aeruginosa* | *Staphylococcus aureus*
 Entrez Protein: <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=protein>
 AbOmpA

FURTHER INFORMATION

Acinetobacter baumannii and other pathogens in injured soldiers: <http://www.acinetobacter.org>
Acinetobacter baumannii MLST database Institut Pasteur, Paris, FR: <http://www.pasteur.fr/recherche/genopole/PF8/mlst/Abaumannii.html>
Acinetobacter baumannii MLST databases University Oxford, UK: <http://pubmlst.org/abaumannii>
 ARDRA for *Acinetobacter* species identification: <http://users.ugent.be/~mvanech/ARDRA/Acinetobacter.html>
 Dutch working party on infection prevention (WIP): <http://www.wip.nl/UK>

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