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Acinetobacter infections – Epidemiology and pathogenesis of a significant healthcare-associated pathogen

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Abstract. The genus *Acinetobacter* contains a heterogeneous array of environmental and commensal organisms. The majority of these strains are non-pathogenic; however, *A. baumannii* has emerged as a common nosocomial pathogen. Groups with the highest risk of *A. baumannii* infection include immunocompromised and critically ill patients, and those undergoing long-term care following severe burns or traumatic injury. In these patients *A. baumannii* can cause wound infections, pneumonia, and sepsis resulting in prolonged recovery time, longer hospital stays, and in some cases can be a contributing factor in mortality. The rise to prominence of *A. baumannii* in the healthcare setting can be attributed to intrinsic resistance to desiccation and chemical disinfectants, which allow the organism to persist on surfaces. This persistence provides a constant reservoir for transmission and can result in recurrent outbreaks within hospital units. Additionally, numerous native antibiotic resistance mechanisms along with the evolution of novel resistance through mutation or horizontal gene transfer has resulted in multi-drug resistant (MDR) strains which demonstrate resistance to nearly every available class of antibiotic. While the development of new antibiotics such as tigecycline holds some promise for treating these resistant strains, the best interventional strategy is to prevent nosocomial spread through the use of screening, contact isolation and good hand hygiene practices.

Introduction

Organisms belonging to the genus *Acinetobacter* have been recognised since the early 1900s, but wide phenotypic variation within the genus has led to repeated taxonomic re-classification.[1] Only with the advent of molecular typing techniques has the genus been well-defined and the taxonomy of its members appropriately classified. *Acinetobacter* spp. display great heterogeneity and range in their ability to utilise carbon sources[2,3] and demonstrate increased resistance to various disinfecting compounds, such as sodium hypochlorite, peracetic acid, H_2O_2 and sodium hydroxide.[4] Although the majority of *Acinetobacter* species are ubiquitous in the environment, the primary pathogen, *A. baumannii*, is rarely isolated outside the healthcare environment.[1,5] This opportunistic pathogen is most commonly implicated in infections in critically ill or immunocompromised individuals undergoing long-term care. The emergence of *A. baumannii* as significant nosocomial pathogen coincided with the use of broad spectrum antibiotics. Intrinsic resistance to chemicals, disinfectants and many classes of antibiotics permits *Acinetobacter* to persist in hospital environments and on surgical instruments, which can become an important source of infection. This persistence further allows for acquisition of additional resistance genes, leading to the emergence of multi-drug resistant (MDR) strains. *A. baumannii* is among the most common of MDR clinical isolates in the United States, Europe and Asia, and is a major threat moving forward.[6,7] This review encompasses a thorough literature review, including 143 primary research publications and review articles, and highlights strain diversity, ecological niches, resistance mechanisms, clinical presentations and effective interventional strategies to cope with *Acinetobacter*, an emerging healthcare-associated pathogen.

Epidemiology

Nomenclature and diversity of strains

Acinetobacter spp. are Gram-negative, plump, short rods which are resistant to decolorisation and often appear in pairs.

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The genus *Acinetobacter* comprises a metabolically diverse group of bacteria that share biochemical and phenotypic features with members of several other genera.[2] This diversity and heterogeneity has historically challenged taxonomists, causing *Acinetobacter* to undergo several phylogenetic reorganisations which are thoroughly discussed elsewhere.[2,8–12] Members of the genus *Acinetobacter* are also non-motile, obligate aerobes which are catalase-positive and oxidase-negative.[9]

Until 1986, the genus *Acinetobacter* contained only two defined species, *A. lwoffii* and *A. calcoaceticus*. With the advent of molecular identification technologies it became apparent that *Acinetobacter* is a highly diverse genus composed of several distinct groups, or genospecies. Automated bacterial identification systems do poorly in identifying and differentiating between *Acinetobacter* species and other non-fermenting bacteria due to the considerable metabolic heterogeneity of strains within each genospecies.[9] Because of this, *Acinetobacter* are often divided into broad groups of saccharolytic or asaccharolytic species. Notable asaccharolytic species include *A. lwoffii* and *A. johnsonii*, as well as numerous other species with a low potential to cause disease. In contrast, saccharolytic species include the important pathogens *A. baumannii*, *A. calcoaceticus*, genospecies 3 and 13TU. These four species, often referred to as the *A. baumannii-calcoaceticus* complex, comprise 85–97% of clinically significant isolates and are responsible for the bulk of serious infections.[10,13–16] They are nearly indistinguishable by metabolic testing and also share very high DNA homology.[17,18] Infection with other, primarily asacchrolytic species, is frequently catheter-related and can often be resolved by removal of the catheter and antibiotic treatment without serious sequellae.[19,20] Finally, the emergence of MDR strains of *A. baumannii* are of major concern in hospital intensive care units (ICUs) where they can cause primary and secondary infections that are increasingly difficult to treat.

Ecological niches

Acinetobacter spp. are ubiquitous in the environment and are commonly isolated from soil, water and sewage.[2,3] The bacteria are commonly found growing in biofilms, or clusters of bacteria encased in an extracellular polysaccharide matrix which increases adhesion to surfaces and provides protection from environmental stresses and desiccation. Heterogeneous biofilms containing *Acinetobacter* and other resistant organisms such as *Pseudomonas* spp. and *Corynebacterium* spp. have been identified in ground water and drinking water systems.[4,21–23]

In addition to environmental sources, *Acinetobacter* is found in association with a variety of host organisms and is commonly isolated from the upper respiratory tract, hands, feet, axilla and groin of humans.[5,24–26] The consortia of *Acinetobacter* species colonising humans can differ based on geographic location, season and length of hospital stay. Interestingly, colonisation appears to be more prevalent during the warmer summer months and in tropical regions of the world.[27,28] Studies in Germany, London and rural India all found between 42% and 55% of healthy individuals to be colonised with *Acinetobacter* spp., which comprised up to 30% of the total microbiota collected from sites on the forehead, arms and toes.[5,26,27] Hospitalised subjects had a higher colonisation rate of ~75%. The majority of skin isolates from both healthy and hospitalised European subjects were *A. lwoffii* (>50%) and *A. johnsonii* (21%), while *A. baumannii* was recovered from <1% of individuals tested.[5,26] In contrast, the most prevalent strains colonising individuals in rural India were *A. haemolyticus* (41%) and *A. calcoaceticus* (15%).[27] These studies suggest that natural carriage of pathogenic species including *A. baumannii* by healthy or sick individuals is rare.

In the healthcare setting, resistance to desiccation and disinfectants allows *Acinetobacter* spp. to persist and remain viable on surfaces for 13–27 days.[29,30] The establishment of biofilms can further hinder cleaning and sterilisation, thus providing a persistent source for nosocomial infection.[4,23] Surfaces commonly contaminated with *Acinetobacter* include computer keyboards, countertops, laryngoscopes, gloves, patient charts, endotracheal connector tubes and bedding.[30–36] Specifically, *A. baumannii* was isolated from 4.3% of computer keyboards used by healthcare workers (HCWs) in proximity to patients.[31] Similarly, a survey of patient charts in a surgical ICU unit found *A. baumannii* to be the most prevalent Gram-negative bacterium, present on 5.5% of charts.[32] With so many inanimate reservoirs in addition to colonised and infected patients, it is not surprising that the hands of HCWs are often contaminated.[30,32,33,36]

Outbreaks and regional prevalence

Since the mid-1980s and early 1990s, infections and outbreaks due to *A. baumannii* have been well-documented in Europe and the United States.[37,38] Further, the prevalence of the MDR phenotype is on the rise. A comparison of infection rates between 1975 and 2003 in the USA reveals significant increases in pneumonia (1.5–6.9%), bloodstream infection (BSI) (1.8–2.4%) and surgical site infection (0.5–2.1%) attributable to *A. baumannii*. Additionally, from 1986 to 2003 increases in resistance to ceftazidime (25–68%), amikacin (5–20%) and imipenem (0–20%) were observed.[39]

Emergence of *A. baumannii* as a hospital-associated pathogen in the South Pacific region and Australia has been much more recent. The majority of severe community-acquired pneumonia due to *A. baumannii* appears to be localised in subtropical regions, including northern Australia and Asia.[40] Reports of pneumonia and secondary BSI as a result of non-MDR *A. baumannii* in Northern Territory, Australia, date back to 1981. Afflicted individuals generally had significant underlying risk factors, including smoking, alcoholism, chronic obstructive pulmonary disease (COPD) and diabetes.[41] In 2002, the emergence of carbapenem-resistant strains of *A. baumannii* was first reported in an Australian hospital. In the following 32 months, 90 unique

isolates were obtained from 67 patients, most of which were in the ICU. The percentage of meropenem-resistance rapidly increased and reached a peak of >95% between January and August 2004.[42] Interestingly, the initial emergence of these strains followed a period of increased carbapenem use in the same hospital. Another ICU-related outbreak of carbapenem-resistant *A. baumannii* was reported in an Australian hospital in 2006.[43] The outbreak spanned a period of nearly a year and involved 41 patients. The reservoirs for the outbreak strain included a variety of surfaces and inanimate objects in patient rooms and throughout the ICU. The outbreak was successfully controlled following a rigorous disinfection protocol using an oxidising disinfectant.[43] Resistant strains of *A. baumannii* have also been isolated from individuals injured in the tsunami that devastated Indonesia in 2004, indicating its emergence in other regions of the South Pacific.[44]

Pathogenesis

Clinical presentations

Acinetobacter spp. are primarily opportunistic pathogens, causing surgical and traumatic wound infections, sepsis, pneumonia, urinary tract infections and meningitis in critically ill and immunocompromised individuals.[45–47] Conditions predisposing to infection by *Acinetobacter* include extended hospital stay, treatment with broad spectrum antibiotics, malignancies, invasive surgeries, mechanical ventilation, and chronic conditions such as COPD.[45,46,48,49] The most common *Acinetobacter* infections are pulmonary and blood stream infections.[50,51] The source of BSIs most often appears to be primary pulmonary infection (42–65%), followed by wound infection (23%) and intravenous catheterisation (9–17%).[45,46,50] The use of ventilators has long been recognised as a major cause of hospital-acquired pneumonia. Ventilator-acquired pneumonia (VAP) has been reported as the source of 84% of nosocomial respiratory infections and pneumonia.[46] Likewise, pneumonia caused by *A. baumannii* is also primarily the result of mechanical ventilation. *A. baumannii* is a leading cause of VAP in some hospital ICUs, accounting for up to 28% of all VAP infections.[47] Historically, it was believed that patients who contracted *A. baumannii* VAP had a significantly worse prognosis (mortality rate of 27% in controls, 43% in cases) than those without VAP.[52] More recent studies suggest no significant association of *A. baumannii* VAP with increased mortality; rather, *A. baumannii* infection may be an indicator of a critically ill or moribund state.[53] Discrepancy between the two studies may reflect differences in treatment regimen or the timely administration of appropriate treatment. Early, appropriate treatment is of critical importance since hospital-acquired pneumonia is often the result of MDR bacteria, including MDR *A. baumannii*. Inappropriate empiric or delayed treatment of hospital-acquired pneumonia has been shown to have a negative effect on patient prognosis.[48,54,55]

Bloodstream infections due to *Acinetobacter* spp. account for ~1.5–2.4% of all reported BSIs in the United States, and *A. baumannii* (86%) is the most frequently isolated species.[39,56] Because of the relatively low incidence of *A. baumannii* BSI, empiric therapy for Gram-negative bacteremia is often directed at more common offenders which are predominantly susceptible to β-lactam/β-lactamase inhibitor combination drugs. This has the potential to result in treatment failure and increase morbidity and mortality in patients with *A. baumannii* BSIs. Patients with BSI due to *Acinetobacter* present with symptoms ranging from persistent fever and mild leukocytosis to severe septic shock.[51] In a large study matching patients with *A. baumannii* BSI to control patients with similar underlying medical conditions (pneumonia, sepsis of different aetiology, intra-abdominal surgery, etc.), those patients with *A. baumannii* BSI had ICU stays on average 9 days longer and total length of hospitalisation 19 days longer than matched control patients without *A. baumannii* BSI.[46] This extended inpatient time is comparable to patients with *S. aureus* BSI.[57] *A. baumannii* BSIs are associated with mortality rates as high as 44% to 52%,[51,58] which is slightly higher than the 20% to 40% mortality reported for Gram-negative sepsis as a whole.[59] However, it can be difficult to unequivocally attribute mortality to *A. baumannii* infection since many of these patients have other underlying diseases.[51,58] Additionally, the increased mortality rate associated with *A. baumannii* BSI is likely at least partially attributable to failed or inappropriate treatment as a result of the MDR of many *A. baumannii* strains (discussed later). Infection with less virulent, less resistant *Acinetobacter* species such as *A. lwoffii*, which are almost exclusively associated with catheter-related urinary tract or bloodstream infection, can most often be resolved by removal of the catheter and a short course of antibiotic therapy.[19,60]

Skin and soft tissue infections account for a small percentage of infections attributable to *Acinetobacter*, and are primarily restricted to patients suffering severe burns or traumatic injury. However, these infections are of increasing prevalence and concern in these two specific populations because of the increased risk for invasive infection by *Acinetobacter*. This phenomenon has been highlighted in frontline and tertiary care military clinics which deal with traumatic war wounds.[61,62] In this setting, *A. baumannii* was recovered in pure culture from lesions histopathology consistent with necrotising fasciitis and osteomylitis.[61–63] This type of skin and soft tissue infection caused by *A. baumannii* can often be recognised by the 'peau d'orange' erythyma preceding development of fasciitis.[61,62] These infections require extensive debridement in addition to antibiotic treatment to resolve the infection.[61–63] Dissemination to the bloodstream is also common in this patient group, occurring in 44% of these infections.[63] Although isolated strains are almost exclusively multi-drug resistant, extended appropriate treatment resulted in >85% survival in one report.[61] Invasive *A. baumannii* infections have also been reported and are on the rise in both military and non-military patients being treated for severe burns.[64,65] In these patients, *A. baumannii* is the most frequently isolated

bacterium (73%), followed by *S. aureus* (71%), in the first 15 days following injury and often persists throughout the term of hospitalisation.[65] In contrast, *Pseudomonas* and *Klebsiella* species are predominant later in the wound recovery process.

Community-acquired *A. baumannii* pneumonia (AB-CAP) remains rare, but infection is associated with a more fulminate course than that seen in hospital-acquired illness. The majority of community-acquired infections occur in individuals with underlying conditions such as long-term smoking and COPD, but reports of infection in healthy individuals are also emerging.[49,66] Symptoms of AB-CAP include rapid and severe bacteremia, pulmonary abscesses, disseminated intravascular coagulation, acute kidney injury and acute respiratory distress.[40,66] These severe symptoms coupled with rapid onset, result in a mortality rate of up to 58% within 8 days of admission. Further, appropriate antibiotic treatment within 12 h of diagnosis did not significantly improve clinical outcome.[49]

Resistance mechanisms

Clinical and environmental *Acinetobacter* isolates possesses an array of antibiotic resistance mechanisms, some of which are intrinsic to all *Acinetobacter* species and others which have been acquired. In addition to antibiotics, resistance to an array of chemical disinfectants is a common characteristic among *Acinetobacter* spp., including *A. baumannii*. It should be noted that MDR is a specific characteristic of *A. baumannii*, while other common species such as *A. lwoffii* are generally more susceptible.[6]

β-lactams are probably the most widely used antibiotics to treat infections caused by both Gram-positive and Gram-negative bacteria. The target of these antibiotics is cell wall synthesis. Resistance to β-lactams can be achieved through selective membrane permeability and the production of β-lactamase enzymes. There are four classes of β-lactamases (A, B, C, D) with different characteristics and spectrums of activity, which are expertly reviewed elsewhere.[67] Representatives of each class are found in *A. baumannii*; however the Class A enzymes appear to be less prevalent (Table 1).[68,69] Class A β-lactamases, including extended spectrum variants (ESBLs) can have activity against a range of β-lactams including penicillin G, amoxicillin, cefazolin, cefotaxime and ceftriaxone. Class B, or metallo-β-lactamases (MBLs), often have the same extended spectrum of activity as Class A ESBLs, but in addition have activity against carbapenems and cephamycins while lacking activity against aztreonam.[70,71] Class C, or AmpC-type β-lactamases, are common in *A. baumannii* and often chromosomally encoded. These enzymes provide low-level resistance to cephalosporins, but can also be inducible or plasmid-encoded, leading to increased expression, higher-level resistance, and more broad substrate activity.[67] The extended spectrum of activity includes the inactivation of the oxyimino cephalosporins (ceftazidime and cefotaxime) and carbapenems (meropenem and imipenem).[72] Unlike class A enzymes, the class B and C enzymes are resistant to β-lactamase inhibitors (clavulanic acid, sulbactam, tazobactam).[67] Class D, or oxacillinase (OXA) type β-lactamases comprise a large group of enzymes containing over 150 unique members.[73] These enzymes can be plasmid or chromosomally encoded and have narrow- or broad-spectrum activity which can include extended spectrum cephalosporins and even some carbapenems.[73,74] They demonstrate reduced activity in the presence of NaCl, a unique property which can be useful in identifying members of the class D β-lactamases.[73,75] These enzymes are naturally occurring in many *A. baumannii* and *P.aeruginosa* isolates, but can also be acquired through genetic exchange.[73] The singular or combined activity of these different classes of β-lactamases results in near-complete or complete resistance of most *A. baumannii* isolates to β-lactam class antibiotics.

Outer membrane protein (OMP) channels, also known as porins, mediate selective membrane permeability based on physical size and hydrophobic character of the porin. Gram-negative bacteria generally possess a wide array of OMPs to accommodate a breadth of different substrates. In contrast, *Acinetobacter* spp. possess only a limited array of OMPs. This has been suggested to contribute to the reduced permeability of the *A. baumannii* membrane, which is ~5% that of *E. coli*.[76] The role of reduced membrane permeability in *A. baumannii* resistance to β-lactams, including the cephalosporins, has been recognised since the early 1990s.[76] Research efforts have begun to characterise OMPs such as OmpA, CarO, OprD, OmpW, which appear to have specificity for different antibiotics (Table 1).[77–81] Reduced expression or complete absence of one or more of these OMPs can confer resistance to one or several antibiotics. In one report, a detailed protein profile of a resistant clinical *A. baumannii* isolate revealed the presence of only two different OMPs.[82] This general mechanism of resistance is effective in conferring reduced sensitivity to β-lactams even in the absence of β-lactam inactivating enzymes (β-lactamases).[83,84]

Efflux pumps are another resistance mechanism involving membrane proteins. These pumps actively reduce the intracellular or periplasmic concentration of antibiotics. *A. baumannii* contains an array of efflux pumps which belong to unique families and have different substrate specificity.[78] One such pump, encoded by the *adeB* gene, shows broad substrate specificity and is implicated in resistance to several different classes of antibiotics, including aminoglycosides, fluoroquinolones, macrolides and sulfonamides.[85] In contrast, *craA* has been identified in a clinical isolate of *A. baumannii* and demonstrates high substrate specificity for chloramphenicol, thus conferring high-level resistance to the drug.[79]

Enzymatic modification of either the antibiotic target or the antibiotic itself is another mechanism of resistance. Three aminoglycoside modifying enzymes (AMEs) are present in *A. baumannii.* They function to prevent aminoglycoside binding to 16S rRNA (rRNA) through modification of the

Table 1. Chemical and antibiotic resistance mechanisms present in *Acinetobacter* isolates

Gene	Antimicrobial(s)	Mechanism	Reference(s)
		β-lactamases	
ampC	Pennicillins, cefalosporins, cefamycins, meropenem	Hydrolysis of β-lactam ring; chromosomal or plasmid-borne resistant to β-lactamase inhibitors	67,72,138
OXA	Cafalosporins, carbapeneums	Hydrolysis of β-lactam ring; chromosomal or plasmid-borne resistant to β-lactamase inhibitors, sensitive to NaCl	73–75
VIM/IMP	Pennicillins, carbapenems, cefalosporins, cefamycins	Hydrolysis of β-lactam ring; integron-associated, resistant to β-lactamase inhibitors	71,139–141
		AME[a]	
aph aac ant	Aminoglycosides	Enzymatic modification; inactivates aminoglycosides, prevents binding to 16S rRNA target. Narrow spectrum resistance to aminoglycosides	86,87
		Target modification	
armA	Aminoglycosides	Methylation of 16S rRNA; prevents aminoglygoside binding. Broad spectrum resistance to aminoglycosides	88–91
gyrA	Ciprofloxacin	Point mutations in DNA gyrase (GyrA); alters ciprofloxacin binding site. Confers low level resistance to ciprofloxacin	92,94–96
parC	Ciprofloxacin, nalidixic acid	Point mutations in topoisomerase (ParC); Alters antibiotic binding site. Confers high level resistance to quinolones	93,94,96
		Efflux pumps	
abeS	Chlorhexadine, benzalkonium chloride, bhloramphenicol, biprofloxacin, erythromycin	Efflux pump; small multidrug resistance (SMR) family	100
adeABC	Chlorhexadine aminoglycosides, fluoroquinolones, macrolides, sulfonamides, tigecycline	Efflux pump; resistance nodulation-cell division (RND) family. Resistance can be increased through mutations leading to overexpression of the pump	85,98,133,142
adeIJK qacE	Chlorhexadine, benzalkonium chloride, parvosol	Efflux pump; RND family	98
amvA	Chlorhexadine, benzalkonium chloride, erythromycin	Efflux pump; major facilitator superfamily (MFS)	99
craA	Chloramphenicol	Efflux pump; MFS superfamily. High substrate specificity for chloramphenicol	79
		OMP[b]*/Porin*	
carO	Imipenem, meropenem	Inactivated (mutated) porin or lack of binding site; prevents uptake of imipenem, meropenem	80,81
ompA	β-lactams, desiccation	Generally low permeability, slow uptake of substrate; limited uptake of β-lactams. Aids establishment of biofilms; prevents desiccation, physical barrier to antibiotics	78,82,143
ompW	Colistin	Reduced expression of *ompW*; reduced uptake of colistin	78
oprD	Imipenem, meropenem	Absent from resistant strains; unable to uptake imipenem, meropenem	77

[a]Aminoglycoside-modifying enzymes.
[b]Outer membrane protein.

antibiotic, thus preventing the inhibition of bacterial protein synthesis.[86,87] Another mechanism of resistance to this class of antibiotics is the modification of the rRNA target itself. This modification is mediated by ArmA, which is often carried on mobile elements, such as plasmids and transposons.[88–91] Unlike AMEs, which may have high activity against only specific aminoglycosides, modification of the rRNA target confers high level broad spectrum resistance to the entire class of antibiotics.[88]

Spontaneous mutation of an antibiotic target can also give rise to a resistant phenotype. This is observed in *A. baumannii* which have acquired mutations in DNA gyrase (*gyrA*) or topoisomerase (*parC*) enzymes (Table 1).[92,93] These enzymes, involved in DNA replication, are targets of the fluoroquinolones. Mutations in *gyrA* alone confer low-level (4 μg/mL) resistance to ciprofloxacin, while strains with secondary mutations in the *parC* gene exhibit higher resistance (64 μg/mL) to ciprofloxacin and nalidixic acid.[92–94] Because resistance correlates well with the presence of specific residue substitutions in one or both of these genes (*gyrA*, *parC*), molecular assays have been developed that can rapidly and accurately identify the resistance genotype and thereby aid in the administration of appropriate treatment.[95,96]

Intrinsic resistance to chemical disinfectants is likely a key factor which also aids in *Acinetobacter* persistence within the hospital environment. Penna *et al*. have noted increased resistance to common biocides including sodium hypochlorite, peracetic acid, H_2O_2 and sodium hydroxide.[4] This may be linked to the ability to form biofilms, which also protect *Acinetobacter* from desiccation.[29] Resistance to common biocides such as benzalkonium chloride, chlorhexidine gluconate and Virkon-S is elevated as much as

8, 6, and 2-fold, respectively, in *A. baumannii* strains growing as biofilms.[97] Further, resistance to these chemicals may be induced in response to exposure to the biocides themselves.[97] The genetic basis of resistance to biocides and disinfectants has begun to be elucidated, and appears to involve genes encoding several efflux pumps belonging to different families (Table 1).[98–100] Each pump demonstrates specificity for a small group of specific substrates while also maintaining low-level activity for a larger group of relatively diverse substrates. The combination of pumps present and/or expressed in different *A. baumannii* isolates and the overlapping activities provide for synergism and contribute to a high level of resistance to chemical biocides observed in some clinical isolates.[98]

Infection control considerations

Transmission of Acinetobacter *in the healthcare setting*

The most commonly isolated strain in hospitals continues to be *A. baumanii*, but less common strains in the *A. baumanii–calcoaceticus* complex such as 13TU and genospecies10 are increasingly implicated in endocarditis and sepsis.[10,13,14] Outbreaks of MDR *A. baumannii* are often the result of a single, clonal strain which serially colonises inpatients or persists on fomites within the hospital environment.[101,102] Specific facilities in which there is a high prevalence of MDR *A. baumannii* carriage include long-term care facilities such as nursing homes and acute care military clinics.[102,103] The association of *A. baumannii* infection with traumatic war injuries was demonstrated during the Vietnam conflict, where it was the most common Gram-negative pathogen isolated from wounds.[104] Similarly, the prevalence of MDR *A. baumannii* infection has been rising in soldiers wounded in the recent Middle East conflict.[62] These strains can be introduced to community hospitals by colonised individuals being transferred from healthcare facilities where MDR *A. baumannii* is endemic and can be a potential source of outbreak.[102]

As discussed, the healthcare environment presents a significant source for acquisition and dissemination of *Acinetobacter* spp., including MDR strains. *A. baumannii* can be disseminated through aerosolisation of droplets or contact with tainted inanimate objects; however, direct contact between colonised or infected patients and the hands of HCWs is the most common mode of transmission.[105,106] In one study, routine interactions with MDR *A. baumannii*-colonised patients resulted in transmittal of MDR *A. baumannii* to the gloves or gowns of attending HCWs in 39% of patient interactions. Further, MDR *A. baumannii* was isolated from the bare hands of HCWs in 5% of interactions despite the use of gloves.[36] This may be due to improper hand washing or incidental contact with used gloves or gowns. Epidemiology based on pulsed field gel electrophoresis (PFGE) analysis of isolates demonstrated that 88% of colonised patients transmitted MDR *A. baumannii* at least once. Therefore, the hands of HCWs represent important mechanisms of nosocomial spread and new infections. Consequently, the importance of good hand hygiene practices is critical to controlling the spread of common nosocomial pathogens, including *Acinetobacter* spp.

A major risk factor for infection is current or prior colonisation of the patient.[107] Other risk factors include use of a ventilator and prior treatment with broad spectrum antibiotics.[46,107] A study which examined VAP found 24% of cases throughout several different wards to be attributable to *Acinetobacter* spp., primarily *A. baumannii*. Molecular fingerprinting demonstrated that the infecting strains were identical to strains found on endotracheal connector tubes or bedrails in ~72% of cases, implicating a nosocomial source of infection.[33] Similar studies have identified 92–100% of bloodstream infections to be attributable to hospital-acquired strains.[50] Thus the most effective way to prevent nosocomial dissemination and acquisition by new patients is to identify colonised patients or other reservoirs and take appropriate measures to prevent further spread of the bacterium.

Screening methods to identify colonised individuals

Due to the difficulty in treating infections and controlling spread of MDR *A. baumannii* through the use of antibiotics, other avenues to curtail dissemination and prevent infection need to be explored. Contact isolation, strict hand hygiene for HCWs, and environmental disinfecting programs have been instituted for inpatients found to be positive for MDR *A. baumannii*. These efforts were able to both control isolated outbreaks and reduce the MDR *A. baumannii* colonisation rate among inpatients by up to 76%.[108–110] The positive impact of these practices has prompted the investigation of different screening techniques to effectively and pre-emptively identify colonised patients in an attempt to prevent spread of this pathogen.

Current screening methods for carriage of *A. baumannii* lag behind those in place for other healthcare-associated pathogens such as methicillin-resistant *S. aureus* (MRSA) and vancomycin-resistant *Enterococcus* (VRE). Unlike MRSA (nares) or VRE (stool) which are reliably present at a high density at one body site, *A. baumannii* can be transient colonizers of numerous body sites including axilla, nostrils, groin, toe webs, forehead and buccal mucosa.[5,26,111] Additionally, colonisation may constitute a low concentration of *A. baumannii* among more numerous resident flora.[5,111] These complications are highlighted by one study in which the sensitivity of detection ranged from 18–29% when swabbing single body sites, and only reached 55% when combining positive results from up to six different sites (Table 2).[112] A recent study employing large sponges for collection of surveillance specimens, coupled with 24-h enrichment in nutrient broth and plating to Modified Leeds *Acinetobacter* medium (mLAM) achieved an increased sensitivity of 89% when sampling only two sites (thigh, upper arm).[113]

Selective and differential chromogenic medium for routine screening of patients has also been developed. Unfortunately, studies of the clinical utility of such media have produced mixed results (Table 2). A small study of critically ill

Table 2. Sensitivity and specificity of different screening methods for detection of *A. baumannii*

Method	Specimen type	Sensitivity (%)	Specificity	Reference(s)
Broth enrichment (BHI, 24h) followed by plating to MacConky agar	Individual swab collection from up to 6 body sites (nostrils, pharynx, skin, rectum, wound, trachea)	55[a]	NR[b]	112
Broth enrichment (NB, 24h) followed by plating to Modified Leeds *Acinetobacter* medium	Combined swab, nostril and groin	66.7	NR	113
	Combined sponge, upper arm, thigh	89.1	NR	
CHROMagar *Acinetobacter*	Stool or perianal swab; direct inoculation	91.7	89.6%	114
CHROMagar *Acinetobacter*	Mixed culture of *A. baumannii* and other typical flora (analytical analysis)	100	75%	115

[a]Combined sensitivity using all sites. Individual site sensitivity ranged from 18% to 29%.
[b]NR; not reported.

patients in an ICU demonstrated high sensitivity (91.7%) and specificity (89.6%) of a chromogenic medium for detecting MDR *A. baumannii* from stool and perianal swabs. However, this study included only 70 patients and all recovered *A. baumannii* isolates were European clone II strains.[114] A study examining a larger cohort identified 22 different *A. baumannii* clonal groups primarily isolated from blood and wound specimens. The authors reported a failure of the medium to effectively differentiate carbapenem-resistant from sensitive strains, as well as allowing the growth of other carbapenem-resistant strains, principally *E. cloacae* and *P. aeruginosa*, which produced similarly coloured colonies to *A. baumannii*.[115]

Microbe-resistant medical devices

Because of the prevalence of *A. baumannii* on medical devices, the use of devices impregnated with antibiotics or with antimicrobial coatings such as silver or copper has been explored. Central catheter lines are a leading risk factor for the development of bacteremia.[116] *In vitro* experiments using catheter lines impregnated with minocycline and rifampin demonstrated a significant reduction in adherence of *A. baumannii* and other pathogens to the impregnated lines.[117] Several commercially available silver-impregnated wound dressings were also evaluated *in vitro* for their antimicrobial activity. Performance of the different dressings varied widely but all achieved some level of antimicrobial activity against *A. baumannii* ranging from 1 to >5 log reduction in viable cell count over 4 h.[118] The use of silver-coated endotreacheal tubes has also been associated with a 60% reduction in mortality in patients with VAP involving MDR pathogens, including *A. baumannii*.[119] A similar approach has been shown to be successful (99.999% reduction in viable cells) when copper-silver ion coatings were investigated as a means to eliminate hardy pathogens such as *P. aeruginosa* and *A. baumannii* from hospital water supplies as a point source for infection.[120] While the cost of these different impregnated or coated devises is significantly greater than similar traditional devices, the overall cost of care for patients treated with these devices (based on reduced length of hospital stay, fewer antibiotics, etc.) can be lower than that of control patients.[121] In the case of ventilators, replacement of internal filters may be necessary to prevent continual seeding of patient rooms and halt further infections with the same epidemic strain.[122] Still, the simplest approach to reduce the spread and prevent new infections due to *A. baumannii* is frequent cleaning and sterilisation of medical equipment and good hand hygiene.[108]

Future perspectives

Future trends in antimicrobial resistance

Broad-spectrum and multiple-resistance phenotypes of many clinical *A. baumannii* isolates have left clinicians with precious few treatment options. Among these are colistin and tigecycline. A 2008 report of 66 MDR *A. baumannii* isolates from patients with VAP found only 25% of isolates to be resistant to tigecycline, and zero resistant to colistin.[123] Colistin has been available since the 1960s but fell out of favour because of reported nephro- and neurotoxicity.[124] However, colistin has found use in critically ill patients infected with MDR Gram-negative pathogens. Tigecycline belongs to a new class of antibiotics, the glycylcyclines, which are structurally and functionally similar to tetracycline but exhibit broad-spectrum activity.[125] In a study including 234 *A. baumannii* clinical isolates, tigecycline exhibited the lowest minimum inhibitory concentration at 90% (MIC_{90}: 1 µg/mL, range: 0.064–4.0 µg/mL) of the antibiotics tested, and sensitivity was independent of the resistance profile of the strain to other antibiotics.[126] Clinical studies evaluating the *in vivo* efficacy of tigecycline in treating MDR *A. baumannii* infections show promising results; however, large case-controlled studies have not been conducted.[127] Unfortunately, although rare, resistance to colistin and tigecycline has been cited. Heteroresistance to colistin was observed in isolates from patients with a previous history of colistin treatment, and was significantly higher than that of isolates from control patients not receiving colistin.[128] Indeed, Adams and colleagues demonstrated induced resistance through serial passage of MDR *A. baumannii* in broth with increasing concentrations of colistin.[129] Similarly, the emergence of tigecycline resistance following treatment of susceptible strains has been reported in *A. baumannii* and *K. pneumoniae* infections.[130–132] Resistance to tigecycline appears to be mediated by point mutations which dramatically increase the expression of the *adeB* efflux pump.[133]

The development of novel antibiotics such as meropenem, doripenem and sitafloxacin have shown some potential for aiding in the treatment of MDR *A. baumannii*.[134,135] Unfortunately, emergence of resistance to these antibiotics is rapid since they are modifications of existing antibiotics to which resistance mechanisms are well established. Therapies containing multiple antibiotics have shown promise in treating MDR strains. Combinational therapy using as little as 1/4 of the established MIC each of doripenem, polymyxin B and rifampin, reduced growth of MDR *A. baumannii* isolates by more than 5000 times that of single or double therapies *in vitro*.[136] A similar study found synergistic antibacterial activity when using cefepime and amikacin, or cefepime and levofloxacin, but not amikacin and levofloxacin.[137]

Regardless of the antimicrobial therapy used in treatment, it seems a safe assumption that resistance mechanisms will arise, thus, novel antibiotic resistance will continue to be a challenge to future antimicrobial therapy.

Conclusion

The emergence of *A. baumannii* as a significant nosocomial pathogen is a prime example of an opportunistic pathogen taking advantage of an increasingly at-risk population. Intrinsic resistance to common disinfectants and the ability to persist on surfaces and form protective biofilms make it difficult to eradicate this bacterium from heathcare settings and provides an easy mechanism for patient-to-patient spread and repeated outbreaks. The presence of an array of native antibiotic resistance mechanisms, as well as the acquisition of specific antibiotic resistance genes through lateral transfer, has resulted in strains of *A. baumannii* that are resistant to nearly every type of drug currently available. Thus, the treatment of resistant *A. baumannii* infections will continue to present a challenge. This underscores the importance of proper infection control measures, including screening, contact isolation and good hand hygiene when interacting with patients colonised or infected with *A. baumannii*.

Conflicts of interest

The authors received no special funding for the composition of this manuscript and declare no conflicts of interest.

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