



## Review

# Control and management of multidrug resistant *Acinetobacter baumannii*: A review of the evidence and proposal of novel approaches

S.E. Weinberg<sup>a</sup>, A. Villedieu<sup>a</sup>, N. Bagdasarian<sup>b</sup>, N. Karah<sup>c,\*\*</sup>, L. Teare<sup>a</sup>, W.F. Elamin<sup>a,d,\*</sup>

<sup>a</sup> Department of Microbiology, Mid Essex Hospital Services NHS Trust, United Kingdom

<sup>b</sup> National University Health System, Singapore

<sup>c</sup> Department of Molecular Biology and Umeå Centre for Microbial Research (UCMR), Umeå University, Sweden

<sup>d</sup> King's College Hospital, Dubai, United Arab Emirates

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## SUMMARY

Hospital-acquired infections are on the rise and are a substantial cause of clinical and financial burden for healthcare systems. While infection control plays a major role in curtailing the spread of outbreak organisms, it is not always successful. One organism of particular concern is *Acinetobacter baumannii*, due to both its persistence in the hospital setting and its ability to acquire antibiotic resistance. *A. baumannii* has emerged as a nosocomial pathogen that exhibits high levels of resistance to antibiotics, and remains resilient against traditional cleaning measures with resistance to Colistin increasingly reported. Given the magnitude and costs associated with hospital acquired infections, and the increase in multidrug-resistant organisms, it is worth re-evaluating our current approaches and looking for alternatives or adjuncts to traditional antibiotics therapies. The aims of this review are to look at how this organism is spread within the hospital setting, discuss current treatment modalities, and propose alternative methods of outbreak management.

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**Abbreviations:** ABC, *A. baumannii* complex; AMP, Antimicrobial peptides; CRAB, carbapenem-resistant *A. baumannii*; EPIC, Extended Prevalence of Infection in Intensive Care study; EU/EEA, European Union (EU) and European Economic Area (EEA) countries; FMT, faecal microbiota transplantation; HPV, Hydrogen peroxide vapour; MDR-AB, Multidrug-resistant *Acinetobacter baumannii*; MDR-GNB, Multidrug-resistant Gram-negative bacteria; MIC, minimal inhibitory concentrations; SOAP, Sepsis in European ICUs study; UVC, UV-C light; XDR, Extensively-drug resistant.

\* Corresponding author. Department of Microbiology, Mid Essex Hospital Services NHS Trust, United Kingdom and King's College Hospital, Dubai, United Arab Emirates.

\*\* Corresponding author. Department of Molecular Biology and Umeå Centre for Microbial Research (UCMR), Umeå University, Umeå, Sweden.

**E-mail addresses:** [nabil.karah@umu.se](mailto:nabil.karah@umu.se) (N. Karah), [wael.elamin@nhs.net](mailto:wael.elamin@nhs.net), [wael.elamin@yahoo.com](mailto:wael.elamin@yahoo.com), [w.elamin@qmul.ac.uk](mailto:w.elamin@qmul.ac.uk) (W.F. Elamin).

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## Introduction

*Acinetobacter* was first isolated in 1911 in Delft, Netherlands, by a Dutch microbiologist, Beijerinck [1], but was not definitively recognized until 1971 [2]. *Acinetobacter* species were initially treatable with antibiotic monotherapy, but high rates of resistance were noted only four years later in 1975 [1]. Over the years resistance rates have increased and in the early 1990s the first reports of carbapenem resistant isolates were documented [3]. Although often still sensitive to colistin, increasingly colistin-resistant isolates have been reported [3,4].

Contamination of mechanical ventilators, hemofiltration machines, cleaning equipment, cleaning fluids, door handles, patient beds, bedside cupboards, and computer keyboards have been reported during outbreaks [5,6]. Guidelines exist on specific measures for detecting and controlling transmission, but despite these guidelines *A. baumannii* continues to cause nosocomial outbreaks [6–12], and the emergence of multi-drug resistant (MDR), and extensively-drug resistant (XDR) strains of *A. baumannii* have further raised the stakes for control of this problematic pathogen.

### Epidemiology and clinical relevance

The *Acinetobacter* genus consists of over 50 species, most of which are ubiquitous in the natural environment, have low pathogenicity and are most commonly found in soil and water [2,12]. Of these, *A. baumannii* is the most well-studied of the genus, due to its notable role in human infections. *A. calcoaceticus*, and *A. baumannii* (among others) are difficult to distinguish by phenotypic tests alone; this group is sometimes termed the *A. calcoaceticus* – *A. baumannii* complex (ABC) and accounts for the vast majority of clinical infections caused by *Acinetobacter* species.

The *A. baumannii* population is clonal in nature. Three of eight described lineages (IC1-3) have been found in nearly all European countries [12]. Many outbreaks have been associated with one of these three major European clonal complexes, with IC2 being the most prevalent [12].

Infections caused by *A. baumannii* include pneumonia, meningitis, bloodstream, and surgical site infections [2,5]; it is also known to colonize patients without causing infection [5]. Clinical infection with *Acinetobacter* in the healthcare setting is often seen in patients undergoing invasive procedures and those with underlying debilitating conditions. Hospital-associated *Acinetobacter* infections are often device-associated, including ventilator-associated pneumonias, and catheter-associated urinary tract infections [7]. Risk factors for colonization or infection with *A. baumannii* include prolonged hospital stay, mechanical ventilation, intravascular devices, advanced age, immunosuppression, admission to an intensive care unit (ICU), recent surgery or invasive procedures, severe burns, and severity of illness [1,2,13].

Tacconelli et al. evaluated risk factors for MDR-AB in intensive care units and medical and surgical wards to determine if risk factors differed between those colonization versus infected [13]. The authors found that the use of third-generation cephalosporins, carbapenems, and broad-spectrum penicillins were associated with an increased risk of nosocomial pneumonia due to MDR-AB. Receipt of  $\beta$ -lactam

antibiotics conferred increased risk for both colonization and infection. Bed-bound status and previous ICU admission were associated with colonization, while the presence of a central venous catheter and surgery were associated with infection. It must be noted that the presence of a central venous catheter reflects the severity of underlying disease, as well as serving as another port for healthcare worker contact.

Among patients who are hospitalized without exposure to the ICU, the skin carriage rate of *Acinetobacter* spp. Has been found to be as high as 75% [2], with the digestive tract identified as a significant reservoir of *Acinetobacter* [7]. These findings are consistent with a large systematic review of the risk factors for the isolation of MDR *A. baumannii* by Falagas [14]. Falagas [14] also noted that environmental contamination was found to be important in nearly 74% of epidemics described (20/27 studies), with contamination of equipment including ventilators, bed rails, and washbasins, with only 20% implicating prior use of broad spectrum antibiotics [14]. The most commonly documented risk factor for culturing MDR *A. baumannii* from wounds is through contact with contaminated environmental surfaces [15] such as around bed sites, trollies, radiators, window sills [16], ultrasound equipment, portable radiograph equipment, medical charts, stethoscopes, shower heads [17], and even mobile phones [18].

In a systematic review of 97 *A. baumannii* outbreaks, when multiple routes of transmission were possible, transmission was found to occur most frequently via direct person-to-person transmission – predominantly through hand contact of healthcare workers, staff, and visitors (76.3%) – as well as indirectly through contact with dry surfaces such as tables, bedframes, and mattresses (59.8%) [19].

Once established in a healthcare environment it is very difficult to eradicate. This is due to *A. baumannii*'s ability to form strong biofilms on both biotic and abiotic surfaces [5,20,21]. Although biofilm-producing bacteria exist in various environments, biofilm-forming *A. baumannii* exist almost exclusively in hospital environments [21]. *A. baumannii* can survive on dry inanimate materials from 3 days to 5 months [19,22] and possesses a hydrophobic ability that provides attachment to foreign material such as plastics used in intravascular devices, catheters, and ventilators [1]. It has been proven that surface hydrophobicity is highly expressed in strains isolated from patients compared to the normal flora of the skin [1]. To survive in these conditions, *A. baumannii* becomes metabolically inactive in the deeper layers of the biofilms. Poor penetration and inability of antibiotics to act on metabolically inert bacteria increases its virulence and pathogenicity [1].

### Resistance and morbidity and mortality

*A. baumannii* possesses an intrinsic carbapenem-hydrolysing oxacillinase OXA-51 that confers resistance to carbapenems only when over-expressed [12]. The most frequent acquired mechanism leading to carbapenem resistance in *A. baumannii* is the production of oxacillinase OXA-23 like, OXA 24/40-like, OXA-58 like, OXA 143-like or OXA 235-like [12].

A recent analysis of the global prevalence of antibiotic resistance in *A. baumannii* infections by Xie et al., (2011–2016) found a prevalence of resistance to imipenem of 73.9–77.8% [4]. This resistance rate increased dramatically from the period of 2000–2005 when resistance was only 23.8% [4].

Colistin resistant *Acinetobacter* was first reported in the Czech Republic in 1999 and has been increasingly reported worldwide [2]. Low levels of resistance have been reported in the UK (2%) [23], and the United States (5.4%) [24]. Higher levels of resistance have been reported in Korea (30%), Spain (40.7%), Iran (48%), and India (53%) [1].

*A. baumannii* is responsible for up to 9% of all Gram-negative bacterial infections in Intensive Care Units (ICUs) in Europe and the United States, according to the most recent Extended Prevalence of Infection in Intensive Care (EPIC II) study published in 2009 [25]. This is considerably higher than the 3.6% reported in the Sepsis in European ICUs (SOAP) study in 2006 [26].

Although resistance to carbapenems is associated with increased mortality, it is difficult to determine the independent influence of MDR *A. baumannii* on morbidity and mortality. This is because many studies are hindered by multiple confounders include the presence of polymicrobial infections [27], inability to differentiate between infected and colonized patients [13], or critical clinical status of patients, among others. Differences in mortality might also be explained by variability in the virulence of *A. baumannii* clones [12].

In the EPIC II study, a multinational study of 14,414 ICU patients, infection with MDR *Acinetobacter* species was independently associated with a greater mortality [25]. This is supported by a systematic review of case-control studies by Falagas et al. [27]. Matched case-control and cohort studies examining the effect of colonization or infection with *A. baumannii* on morbidity and mortality were reviewed; they provided evidence that MDR *A. baumannii* infections are associated with a mortality rate in excess of 24% [27]. Other studies report a crude mortality rate of 26%–52% [1,9] and have been shown to increase the mortality rate by up to 22% in ICU patients [9].

The EPIC II study also recognized the considerable variation in the types of organisms isolated from different geographical regions, with *Acinetobacter* incidence ranging from 3.7% in North America, to 19.2% in Asia [25]. The rapid increase of antibiotic resistance is likely multifactorial, but may in part be due to the spread of already established clones from the transfer of patients, travellers, medical tourism, and refugees from regions where antibiotic resistance is higher [4]. Geographical areas with a high prevalence of carbapenem-resistant *Acinetobacter baumannii* (CRAB) are south and south-east Asia, south America and the Middle East [12]. Moreover, transmission of such strains between hospitals and departments has been observed, most likely via transfer of asymptomatic colonised patients [12,17,28,29] or healthcare workers [29]. Cross-border transmission also occurred with repatriation of war casualties previously from Iraq and Afghanistan [1,12,21]. In studies of outbreaks of other multidrug resistant organisms it has been shown that isolation of infected patients on admission is often insufficient to prevent the spread of infection [28].

### Strategies for control

In 2006 and 2007, the Healthcare Infection Control Practices Advisory Committee and the Centres for Disease Control and Prevention (CDC) published guidelines for the management of multidrug-resistant organisms and the use of isolation precautions in healthcare settings [30], and in 2008 the Department of Health UK rolled out a comprehensive hospital deep cleaning programme along with a new national specification for

hospital cleanliness [31]. These programs introduced care bundles (i.e infection control guidelines for invasive lines, ventilators, catheters), deep cleaning protocols, cohorting of patients, and improved screening measures [31].

Despite these measures, in 2011 the European Antimicrobial Resistance Surveillance System Network (EARS-Net), which includes 29 European countries, reported a general European-wide increase of antimicrobial resistance in Gram-negative pathogens under surveillance [22]. In the USA, data reported to the CDC National Nosocomial Infection Surveillance System and National Healthcare Safety Network reflected an increase in the rates of infections caused by multidrug-resistant Gram-negative bacteria (MDR-GNB), with 65% of all *A. baumannii* isolates meeting the MDR criteria [22].

The infection prevention and control (IPC) measures applied in hospitals for MDR-GNB varied widely both within and between different countries. In 2013 the European survey on carbapenemase-producing *Enterobacteriaceae* (EuSCAPE) project highlighted the fact that surveillance and reporting of CRAB cases were not routinely performed in all European Union (EU) and European Economic Area (EEA) Countries. Only 21 out of 30 EU/EEA countries performed surveillance of CRAB and only 2 countries had any national recommendations or guidelines on IPC measures to prevent the spread of CRAB [12]. Between 2012 and 2015, however, the number of countries reporting data on *Acinetobacter* to EARS-Net increased from 18 to 30 (i.e. all EU/EEA) countries, and by 2015 12 countries had implemented national IPC recommendations or guidelines, with six more not yet published [12]. In 2018 EARS-Net reported that more than half of the *Acinetobacter* species isolates were resistant to at least one of the antimicrobial groups (56.7%). Large inter-country variations were noted for all antimicrobial groups with higher resistance percentages reported from southern and eastern Europe, compared with northern Europe [32]. Of all the microorganisms under surveillance by EARS-Net, *Acinetobacter* is the one for which there exists the most inter-country variation in resistance percentages, with a range between 0% and 96.1% depending on the reporting country [32].

There are many reports of successful control and eradication of MDR *A. baumannii* using a combination of techniques [5,15,17,30]. However, current management of *Acinetobacter baumannii* prevention, infection and outbreaks is based on observational studies and pharmacodynamic modelling [33]. And while the various guidelines contain broad areas of agreement, there are some inconsistencies between the guidelines, reflecting the limited evidence available in the published literature [10]. Management is based around source control, including antibiotic stewardship, hand hygiene, contact precautions, education and effective environmental cleaning [22,33]. Several studies suggest closure of hospital units may be necessary to control an outbreak [33,34]. This can come at a great cost: the cost of an outbreak of *A. baumannii* is estimated on average at 266,500 GBP (350,000 USD) [9,11], the largest cost being associated with lost bed days through extended patient stays or ward closures, and which can result in reduced capacity to perform elective surgical procedures due to bed closures [11,34].

### Hand hygiene and contact precautions

*A. baumannii* has been found to be the most frequent Gram-negative species causing persistent contamination of the hands

of healthcare workers, regardless of the frequency of hand washing [8], with an estimated 20–40% of nosocomial infections attributable to cross-infections via healthcare personnel hands [18]. Even with donning of gloves, hand contamination has been reported at 4.5% for healthcare workers caring for colonized patients [22]. Contamination of gowns and gloves with MDR *A. baumannii* has been observed in 11–12% of healthcare workers caring for colonized patients [22] and it has been shown that the gloves or hands of healthcare workers are equally likely to become contaminated from touching a patient as touching an environmental surface in a patient's room [35].

In mathematical models of the impact of interventions against *A. baumannii* transmission, hand hygiene was found to be the most effective intervention, because it limits both the transmission between patients and, between patients and the environment [36]. However, despite its efficacy, simplicity, and low cost, hand hygiene is frequently found to have variable adherence from 4–100% compliance [37]. Non-adherence is found to be higher in ICUs compared to other settings, with a median of 30–40% and lower among physicians than nurses [38]. Studies showing the adequacy or inadequacy of hand cleansing found that using only 1 mL of liquid soap or alcohol-based hand rub yielded a greater number of bacteria remaining on the hands than using 3 mL of product to clean hands [37]. This has clinical relevance since some health care workers use as little as 0.4 mL of soap to clean their hands, and on average alcohol-based hand rub dispensers dispense on average 1.5 mL of handwash [37].

It is not known to what extent sink usage for hand hygiene encourages sink contamination or aerosolization from back-splash, but investigations of pathogens from sinks and surrounding surfaces have demonstrated indistinguishable strains, and sinks have been identified as reservoirs [17,22].

Education is essential to convince all personnel about the epidemiological importance of hand hygiene in the control of MDR-AB outbreaks [22,33,37]. Equally it is important to involve public health resources to support the initiation of IPC interventions and infrastructure within hospitals.

In vitro studies of the effectiveness of hand-cleansing agents (plain liquid soap, 70% ethyl alcohol, 10% providone-iodine, or 4% chlorhexidine gluconate) for the removal of hospital strains of *Acinetobacter baumannii* from artificially contaminated hands suggests that 70% ethyl alcohol and 10% providone-iodine may be the most effective hand-cleansing agents for removing *A. baumannii* from heavily contaminated hands [39]. Data shows that alcohol-based hand-rubs could reduce *A. baumannii* counts by 98% from experimentally contaminated hands [22].

Clothing of HCW can also be contaminated by nosocomial pathogens. In particular, gown contamination with MDR-AB has been observed in 11–12% of HCW when caring for colonized patients [22]. Protective clothing, particularly plastic aprons have been associated with a reduction in clothing contamination in high-risk settings such as burn units [22].

In addition to basic IPC precautions (hand hygiene, personal protective equipment, single-use or patient-dedicated non-critical care equipment) consideration for isolation of patients to isolation wards, separate rooms, or cohort nursing care for CRE-colonized patients has shown improved outcomes [22]. However, cohorting of patients relies on a well-established active screening culture, which are not yet well determined. Studies have shown that it may be difficult to detect the

carriage of *A. baumannii* by routine methods, with a reported undetected ratio of 50% among ICU patients [40]. This may be because the best body site for screening has not been well determined. The Association for Professionals in Infection Control and Epidemiology (APIC) guide for the control of MDR-AB suggests culturing multiple patient sites including the nose, throat, axilla, groin, rectum, open wounds and/or tracheal aspirates [7]. The most sensitive site with the highest negative predictive value for detecting MDR-GNB, including MDR-AB was found to be the groin. However, sensitivities of single sites ranged from 13.5 to 29% [40], indicating that the sensitivity of surveillance cultures is low, even when six different body sites are sampled [22].

### Environmental cleaning

The difficulty in eradicating *Acinetobacter* from the environment, even after terminal cleaning, may be due to the presence of dry surface biofilms [18,41]. For instance, Manian *et al.* [6] reported that even after four rounds of terminal cleaning and disinfection with 0.52% sodium hypochlorite solution (1:10 dilution of household bleach), 26.6% of rooms newly vacated by patients with MDR *A. baumannii* had at least one positive culture site, predominantly found in areas of increased patient contact such as pillows, beds, and wheelchairs. There were also positive culture sites in areas with a lower likelihood of direct patient contact but a high likelihood of contact with healthcare staff, such as the interior of cabinets, medication drawers, and keyboards [6]. Multiple studies have demonstrated less than 50% of room surfaces were effectively cleaned following terminal cleaning, leading to an increased risk of 39–353% of acquiring a nosocomial infection for patients admitted to a room where the previous occupant was colonized or infected with a multidrug-resistant pathogen [41,42]. One reason for this might be the possibility that the frequent use of disinfectants such as chlorhexidine, pentamidine, and ammonium compounds has led to strains less susceptible to these agents [43]. As shown by Liu *et al.* different disinfectant concentrations and action times could produce different cleaning effects [44]. This may be due to the presence of disinfectant resistance genes such as gene *qacE* and *qacEΔ1* [43]. In a study of carbapenem-resistant strains of *A. baumannii* (CRAB) isolated from an ITU in Wuhan University People's Hospital, the minimal inhibitory concentrations (MIC) showed a 2-fold increase in the MIC of BB and CHG compared to the susceptible strain in 78% and 64% of isolates respectively, and up to 4-fold increase in 2.5% and 29% of isolates [43]. This is an important area of study as a high concentration of disinfectants increases hospital costs, but can also have long-term toxic effects on patients [45].

Touchless technologies such as aerosolized or vaporized hydrogen peroxide or continuous or pulsed UV-C light (UVC) attempt to overcome some of the deficiencies of manual cleaning by removing the human element [42]. In a meta-analysis comparison of devices, UVC devices were found to be more efficacious in studies with *in vitro* experimentally placed bacteria, but were still unable to effectively penetrate all areas of the patient room [42]. Hydrogen peroxide vapour (HPV) was found to inactivate 100% of the biological indicators, whereas aerosolized hydrogen peroxide (aHP) inactivated 10–79% [42]. However, on review of the efficacy of HPV and aHP use in hospital outbreaks of MDR *A. baumannii*, success has

been mixed, with recurring incidents reported within 4 weeks–8 months [42]. This is likely because of the complex surfaces and devices in a hospital room that harbour reservoirs for pathogens that even touchless methods are unable to completely eradicate [42].

Patient privacy curtains have been implicated in their role in *Acinetobacter* outbreaks [46], either through direct contact with hands of healthcare workers [47], or through airborne dispersal when moved [47]. Within one week of use, over 90% of privacy curtains are found to be contaminated with multidrug-resistant organisms [47,48]. Antimicrobial curtains are one strategy proposed by other authors with mixed outcomes [47,48]. Although one study reported with the use of quaternary ammonium chlorides plus polyorganosiloxane impregnated curtains, the median time of first contamination can be extended from 5 days (standard curtain) to 19 weeks [47], the use of built-in-silver curtains [47] or the use of halamine (Bio-smart) curtains [48] showed no reduction in the microbial burden, and no statistically significant decrease to time to contamination respectively compared to standard privacy curtains.

Decolonization strategies for prevention of infections due to Gram-positive and Gram-negative organisms, such as topical (skin), nasal, and oral decolonization have been suggested to help mitigate hospital-acquired infections [49]. Decolonization through chlorhexidine baths has been an effective tool for mitigating morbidity and mortality from infections due to methicillin-resistant *S. aureus* (MRSA) [50]. One study of chlorhexidine bath use in an ICU outbreak of *A. baumannii* showed a 53% reduction in incidence [20], while Gray *et al.* hypothesized prompt resolution of an outbreak in Canada using this strategy as part of a comprehensive outbreak control strategy [20]. However, this strategy is not recommended by the ESCMID-EUIC guidelines as evidence is insufficient for its use with CRAB [50].

Despite all of these interventions the relative efficacy of IPC interventions are still found to be insufficient [31], and further statistical analyses have revealed that fatal infections are increasing despite more efficient cleaning practices, suggesting that our current procedures are inadequate to protect susceptible patients from serious infections [51].

## Treatment

### Antimicrobial therapy

*A. baumannii* empirical coverage is recommended in severe infections occurring during an *A. baumannii* outbreak or in endemic situations or previously colonized patients [33]. Carbapenems are thought to be the drugs of choice for infections caused by *A. baumannii* in areas with low rates of resistance, but should not be used as monotherapy for severe infections in areas with high rates of resistance [33]. Although there is no consensus recommendation for the optimal treatment of MDR-AB infections, colistin is currently used as the backbone of therapy, despite its nephrotoxic effects [52,53]. It is suggested as part of empirical therapy in patients with high suspicion of/proven carbapenem resistant *A. baumannii* [33]. The efficacy of colistin in severe infections caused by *A. baumannii* has been demonstrated in several retrospective series or case reports [1,52]. Due to colistin having low penetration into the

pulmonary epithelial lining fluid with IV administration (due to its physiochemical properties), the use of inhaled colistin in conjunction with IV colistin is becoming increasingly popular as a way to reduce the nephrotoxic effects associated with high doses of IV colistin [54]. These studies evaluated colistin mostly in directed therapy, but information about its use in empirical therapy is rather scarce. Other agents such as tigecycline and sulbactam should not be used as monotherapy for empirical therapy, but are proven to use in combination with colistin, although controversy remains regarding the most effective combinations [52,53]. A recent systematic review reported colistin in combination with other antibiotics was significantly associated with a higher microbiological cure rate versus colistin monotherapy [52]. Combination therapy is also associated with higher rates of 14-day survival and eradication [53], and a decrease in all-cause mortality [52].

### Human microbiome restoration

Research into bacterial interference in non-epidemic situations was trialed in 1967 in attempt to halt epidemics in newborn nurseries of virulent species of *Staphylococcus aureus* through deliberate introduction of interfering strains of low virulence *S. aureus* 502A [55,56]. Despite its effectiveness in more than 4,000 infants, following a fatal infection of a newborn the “routine” use of bacterial interference programs in non-epidemic situations was halted [55,56]. This project was well ahead of its time, but can provide useful evidence and support for potential areas of further research in the use of recolonization therapy with non-virulent microbes.

The best example of microbiome restoration is faecal microbiota transplantation (FMT) which has become increasingly accepted as a safe and effective intervention for the management of *Clostridium difficile* infection [57], with some studies demonstrating an efficacy with 91% primary cure rate and 98% secondary cure rate [58]. The potential benefit of FMT as a decolonization strategy for MDR-GNB has been tested in several studies with a high level of heterogeneity [50]. Multiple case reports have also shown the use of FMT for the eradication of VRE [59] and Carbapenem-resistant *Klebsiella pneumoniae* [60]. Although evidence is insufficient for or against the recommendation of use of FMT by the ESCMID, evidence thus far is optimistic and warrants further studies to evaluate its effectiveness, applicability and safety in intestinal decolonization of *Acinetobacter* and other Gram-negative bacteria [50,61].

Although the use of microbiome transplantation has not been researched as a mechanism of infection control or treatment for *Acinetobacter*, the use of probiotics and synbiotics is gaining interest. Clinical evidence on the efficacy of probiotics in reducing infections is inconclusive, but has shown to be beneficial in some studies [62]. In a study of the protective effect of synbiotics against MDR-AB in a murine infection model in the probiotic-treated group both weight loss and mortality were significantly attenuated compared to those in the control group, and yielded stable intestinal colonization [62]. Other examples of successful disease modification have been reported such as the use of the probiotic *Lactobacillus* in the inhibition of *Staphylococcus epidermidis* [63], *Corynebacterium* sp. (strain Co304) implantation into the nares of *S. aureus* carriers [64], and the administration of synbiotics following treatment with vancomycin for fulminant MRSA enterocolitis in an infant [65].

The majority of systemic bacterial infections are caused by endogenous pathogens from human microbiota [66]. When undergoing surgery, immunosuppression, or following trauma, those colonized with multidrug-resistant organisms are at a substantially higher risk of difficult to treat infections. *A.baumannii* infections have been found to occur more frequently in patients with fecal colonization than in those without fecal colonization [67]. Many pharmaceutical companies have been reluctant to pursue decolonization agents because of worries that such drugs may not have sufficient market potential to justify cost of development, despite the proof that Mupirocin has reached annual sales of more than \$120 million, proving economic viability [61]. New classes of antibiotics are unlikely to become available in the next few years, thus it may be increasingly important to integrate therapeutic agents with decolonization therapies.

### Antimicrobial peptides

Antimicrobial peptides (AMPs) may be an interesting alternative to antibiotics. We already use the AMP Colistin (Polymyxin E) produced by *P. polymyxa* var. *colistinus*, as a first line agent against MDR-AB, although its use is limited by side effects of nephrotoxicity and increasing rates of resistance [68]. Several other peptides having in-vitro activities against *A. baumannii* have been reported in animal models of infection such as the use of AMP LL-37, a human AMP, or WAM-1, a marsupial AMP [69]. In a study by Spencer *et al.* of the effects of AMP LL-37 and WARM-1 on multidrug resistant *Acinetobacter baumannii*, both peptides were able to inhibit biofilm formation in all clinical isolates at some concentrations, and WAM-1 dispersed mature biofilm in most isolates [69]. Although in the presence of human serum, the antibacterial effects of LL-37 are diminished, this is not the case in studies of WAM-1, which has been shown in vitro to be 12 to 80 times more effective than LL-37 in its ability to kill several bacterial pathogens, including several clinical isolates of *A. baumannii* [69]. It is also resistant to inhibition by high salt concentrations and non-haemolytic, indicating that it may be promising for in vivo applications [69]. Other studies reported on the use of specifically targeted AMP, C16G2 to selectively eradicate *Streptococcus mutans* in the treatment of dental decay along with a reduction in *S. mutans* populations, Guo *et al.* also identified a significant promotion in the diversity and abundance of health-benefiting *Streptococcus* spp following AMP use [70]. Such reports encourage further research into the field for its beneficial effect on the targeted microbe and population shift. Factors such as cytotoxicity, enzymatic degradation, and cost effectiveness still need to be evaluated prior to their systemic use as an antibiotic [1], but are a promising avenue of research in the fight against MDR *Acinetobacter*.

### Bacteriophage therapy

A potential alternative management for treating infections with MDR *A. baumannii* is the use of bacteriophage therapy. Although phage therapy has been around since 1917, it was largely abandoned after World War II following the discovery of broad-spectrum antibiotics [71]. Now, with the increase in antibiotic resistant bacteria, there is renewed interest in the use of phages to treat multi-drug-resistant organisms [72]. The

first report of isolation and characterization of phages against *A. baumannii* was published in 2010 [73].

Although the use of phages is limited by the ability of bacteria to develop resistance to them, the bacteriophages may in turn adapt and regain their infectious abilities [74]. Additionally, the genetic trade-off for bacteria to evolve a trait that improves resistance to antibiotics may make them more susceptible to phage infection, or alternatively, increased phage resistance may force increased sensitivity to chemical antibiotics, and may therefore be best used in combination with antibiotics [72,75]. In a study by Li-Kuang Chen *et al.* of 24 active phages capable of infecting *A. baumannii*, the authors found that the risk of phage infection was significantly increased in antibiotic-resistant strains (84%) when compared to antibiotic sensitive strains (56.5%) [72].

Combined phage and antibiotic therapy has also been shown to result in reversion to antibiotic-sensitive phenotypes, as seen in studies with *Pseudomonas fluorescens* SBW25 and MDR *Pseudomonas aeruginosa* [74,75]. A study by Chan *et al.* [75] demonstrated specific phage selection towards MDR *P. aeruginosa* resulted in increased antibiotic sensitivity. This method allowed for renewed use of historically effective antibiotics when used in combination with bacteriophages [75]. Although these studies were not specific to MDR *A. baumannii*, the principle is likely to be the same.

### Conclusion

*A.baumannii* has emerged as a nosocomial pathogen that exhibits high levels of resistance to antibiotics, and remains resilient against traditional cleaning measures with resistance to Colistin increasingly reported. Given the magnitude and costs associated with hospital acquired infections, and the increase in multidrug-resistant organisms, it is worth re-evaluating our current approaches and looking for alternatives or adjuncts to traditional antibiotic therapies.

It is unlikely that we will be able to enforce narrow spectrum prescribing on an international community, or limit international spread of MDR organisms, including *A. baumannii*. We should therefore consider new approaches to control the spread of MDR *A. baumannii* with the use of promising emerging solutions, such as bacteriophages, AMP, or recolonization therapies in adjunct to advanced cleaning strategies.

### Ethics approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

### Availability of data and materials

Not applicable.

### Conflicts of interest

The authors declare that they have no competing interests.

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## Authors' contributions

All authors read and approved the final manuscript.

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