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EDITORIAL

Michael S. Niederman
Marin H. Kollef

The road forward in the management of *Acinetobacter* infections in the ICU

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M. S. Niederman (✉)
Weill Cornell Medical Center, 425 E. 61st St, New York, NY 10065, USA
e-mail: msn9004@med.cornell.edu

M. H. Kollef
Washington University, St Louis, MO, USA

Acinetobacter spp. infection is a global problem in ICUs, causing a variety of infections and presenting a challenge to effective therapy, because it is often a multidrug-resistant organism, that can lead to adverse patient outcomes. In the EPIC II point prevalence study of ICU infection, *Acinetobacter* spp. accounted for 8.8 % of all ICU organisms, with rates as high as 19 % in Asia and 17 % in Eastern Europe [1]. In one study of Asian ICUs, in patients with nosocomial pneumonia, *Acinetobacter* spp. infection was the most common cause of VAP, accounting for 36.5 % of all episodes overall, and nearly half of all episodes in Thailand [2]. Most of the clinically relevant ICU infections with this organism come from the *Acinetobacter baumannii* group of organisms. As the frequency of this infection has been rising, our therapeutic options have remained limited, and carbapenems (excluding ertapenem, which is not active against this organism) have been the drug of choice for these organisms, but are less effective than in the past, as resistance to these agents rises. Consequently, we have been forced to resort to therapies with polymyxins, and combinations of other agents (including sulbactam and tigecycline).

It is against this backdrop that we welcome the recent publication in *Intensive Care Medicine* of a multinational, multispecialty consensus statement on the management and prevention of *A. baumannii* infection in the ICU [3]. The document is well organized and offers evidence-graded recommendations on the laboratory diagnosis of infection, the approach to therapy for established infection, and the methods for infection control that can lead to prevention and mitigation of outbreaks with this organism.

Much of the confusion in managing *Acinetobacter* spp. infection comes from the limited therapeutic options, and the consensus statement provides useful information. The authors propose that empiric therapy for this organism be provided when an infection develops in an ICU with a high prevalence of this pathogen, or if a patient has been previously colonized. This is consistent with several recent studies. For example, Nseir and colleagues found that occupying an ICU room that previously housed a patient with *Acinetobacter* infection or colonization raised the likelihood of the subsequent patient in that room acquiring *Acinetobacter* by an odds ratio of 4.2 [4]. ICU ecology also had an impact on the bacteriology of VAP in another study [5]. In that study, 152 patients had early onset VAP with no classic risk factors for resistance, yet 50.7 % harbored multidrug-resistant pathogens, including 15.8 % with *A. baumanii*. The authors identified that one risk factor for acquiring these organisms was hospitalization in an ICU with more than a 25 % incidence of multidrug-resistant pathogens. The impact of environmental exposure and environmental contamination is an important consideration in determining the bacteriology of infection and in choosing empiric therapy in the ICU, and the topic of environmental cleaning to prevent *Acinetobacter* infection is also discussed in the consensus statement.

The statement does suggest that if *Acinetobacter* is being treated in an ICU with a low rate of resistance, then

a carbapenem should be used, generally as a single agent. If however, *Acinetobacter* resistance is common, then they recommend using a multidrug regimen that includes a polymyxin, and maybe also a carbapenem, sulbactam, and/or tigecycline. The role of combination therapy in *Acinetobacter* infection is complex, and the authors do not recommend its use in directed therapy, but do acknowledge the benefit of combination regimens for empiric therapy when high rates of resistance are present, or when agents like sulbactam or tigecycline are used. The authors pay particular attention to dosing and pharmacokinetics in recommending specific therapies and the potential benefit of prolonged infusions of carbapenems, sulbactam, and polymyxins. They also consider the potential benefit of adjunctive aerosolized polymyxin in the therapy of highly resistant pathogens, and in patients with a poor response to systemic therapy, but do not consider if this adjunctive therapy should be used routinely. The role of tigecycline in *Acinetobacter* infection is evolving, and it may be necessary to use higher doses than in the past. The consensus statement recommends a loading dose of 200 mg and a daily dose of 100 mg twice daily for the therapy of nosocomial pneumonia, although this is an unapproved dose. However, the prior failures of tigecycline monotherapy in VAP did involve lower doses, and a recent proof of concept study showed that higher doses are feasible and reasonably well tolerated [6, 7]. However, with multidrug-resistant *Acinetobacter*, and tigecycline MIC values greater than 2 μg/ml, tigecycline-based regimens are less effective than colistin-based regimens [8]. Several new therapies for this pathogen are in development, but are not discussed in the consensus statement, One important therapeutic decision that is also unresolved is duration of therapy, and the consensus statement recommends 2 weeks for severe infections such as VAP and severe sepsis, acknowledging that more data are needed in this area.

Prevention of infection and infection control are also an important focus in the consensus statement. The authors recommend contact precautions whenever a patient harbors this organism, and also they recommend activating a high level of alert and awareness whenever a patient has this organism, focusing on cohort isolation, hand hygiene, and environmental decontamination. In the setting of an outbreak, they also recommend the use of surveillance cultures, using weekly rectal and pharyngeal swabs, and tracheal aspirates from intubated patients. The authors point out that in a true epidemic situation, "it takes a village", and there must be full cooperation throughout the hospital, from the doctors and nurses, all the way up to the hospital administration.

The current consensus statement is a good step forward. It organizes what we know and provides practical recommendations for current management. Like all good statements of this type, it is evidence graded, so that we know the strength of the current knowledge base and, most importantly, the agenda for future research (Table 1).

Table 1 Research agenda for *Acinetobacter* infection

Define the role of new diagnostic methods in optimizing early therapy of infection and control of epidemics
Determine the clinical relevance of heteroresistance
Define the best empiric therapy regimens when multidrug resistance is likely
Define the optimal duration of therapy for sensitive and resistant pathogens
Determine if routine adjunctive aerosol therapy is valuable
Determine the optimal dosing and infusion methods for *Acinetobacter* therapy, especially pneumonia
Better identify the role of combination therapy in empiric and definitive management strategies
Optimize methods of environmental decontamination

Compliance with ethical standards

Conflicts of interest None.

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José Garnacho-Montero
George Dimopoulos
Garyphallia Poulakou
Murat Akova
José Miguel Cisneros
Jan De Waele
Nicola Petrosillo
Harald Seifert
Jean François Timsit
Jordi Vila
Jean-Ralph Zahar
Matteo Bassetti

Task force on management and prevention of *Acinetobacter baumannii* infections in the ICU

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J. Garnacho-Montero (✉)
Unidad Clínica de Cuidados Intensivos, Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen del Rocío, Seville, Spain
e-mail: jgarnachom@gmail.com

G. Dimopoulos
Department of Critical Care, University Hospital ATTIKON, Medical School, University of Athens, Athens, Greece

G. Poulakou
4th Department of Internal Medicine, Athens University School of Medicine, Attikon University General Hospital, Athens, Greece

M. Akova
Department of Infectious Diseases, Hacettepe University School of Medicine, Ankara, Turkey

J. M. Cisneros
Unidad Clínicia de Enfermedades Infecciosas, Microbiología y Preventiva, Instituto de Biomedicina de Sevilla (IBIS), Hospital Universitario Virgen del Rocío, Seville, Spain

J. De Waele
Department of Critical Care Medicine, Ghent University Hospital, De Pintelaan 185, 9000 Ghent, Belgium

N. Petrosillo
2nd Infectious Disease Division, National Institute for Infectious Diseases 'L. Spallanzani', Rome, Italy

H. Seifert
Institute for Medical Microbiology, Immunology and Hygiene, University of Cologne, Cologne, Germany

H. Seifert
German Centre for Infection Research (DZIF), Partner Site Bonn-Cologne, Bonn, Germany

J. F. Timsit
Medical and Infectious Diseases ICU, Bichat Hospital, 75018 Paris, France

J. F. Timsit
University Paris-Diderot - Inserm U1137 - IAME, 75018 Paris, France

J. Vila
Department of Clinical Microbiology, CDB, Hospital Clínic, School of Medicine, University of Barcelona, Centre for International Health Research, (CRESIB-Hospital Clínic), Barcelona, Spain

J.-R. Zahar
Unité de Prévention et de Lutte Contre les Infections Nosocomiales, Université d'Angers, Centre Hospitalo-universitaire d'Angers, Angers, France

M. Bassetti
Infectious Diseases Clinic, Santa Maria Misericordia University Hospital, Udine, Italy

Abstract *Introduction:* *Acinetobacter baumannii* constitutes a dreadful problem in many ICUs worldwide. The very limited therapeutic options available for these organisms are a matter of great concern. No specific guidelines exist addressing the prevention and management of *A. baumannii* infections in the critical care setting. *Methods:* Clinical microbiologists, infectious disease specialists and intensive care physicians were invited by the Chair of the Infection Section of the ESICM to participate in a multidisciplinary expert panel. After the selection of clinically relevant questions, this document provides recommendations about the use of microbiological techniques for identification of *A. baumannii* in clinical laboratories, antibiotic therapy for severe infections and recommendations to control this pathogen in outbreaks and endemic situations. Evidence supporting each statement was graded according to the European Society of Clinical Microbiology and Infection Diseases (ESCMID) grading system. *Results:* Empirical coverage of *A. baumannii* is recommended in severe infections (severe sepsis or septic shock) occurring during an *A. baumannii* outbreak, in an endemic setting, or in a previously colonized patient. For these cases, a polymyxin is suggested as part of the empirical treatment in cases of a high

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suspicion of a carbapenem-resistant (CR) *A. baumannii* strain. An institutional program including staff education, promotion of hand hygiene, strict contact and isolation precautions, environmental cleaning, targeted active surveillance, and antimicrobial stewardship should be instituted and maintained to combat outbreaks and endemic situations. *Conclusions:* Specific recommendations about prevention and management of *A. baumannii* infections in the ICU were elaborated by this multidisciplinary panel. The paucity of randomized controlled trials is noteworthy, so these recommendations are mainly based on observational studies and pharmacodynamics modeling.

Keywords *Acinetobacter baumannii* · Epidemiology · Treatment · Colistin · Prevention

Introduction

Acinetobacter baumannii has become a nightmare in many intensive care units (ICU) worldwide. This pathogen is a major cause of nosocomial infections affecting mainly patients admitted to the ICU, although spread to regular wards and to long-term care facilities has also been described. It is characterized by its great persistence in the environment, enabling it to spread rapidly and to have an extraordinary capability to develop resistance to all conventional antimicrobials and some biocides [1, 2]. *A. baumannii* exhibits a wide variety of mechanisms of resistance to antimicrobial agents (Table 1 of the ESM).

In 2007, in a prevalence study of infections in intensive care units (EPIC II) conducted in the five continents, *A. baumannii* was the fifth most common pathogen but with wide variations between countries [3]. In an observational study of ventilator-associated pneumonia (VAP) across Europe, *A baumannii* was the third most common pathogen only after *S. aureus* and P. *aeruginosa* [4]. In a multicentre cohort study conducted in 24 countries, *A. baumannii* was the pathogen most frequently identified in hospital-acquired bloodstream infections [5].

Justification of the project

Considering the high frequency of infections in many ICUs around the globe caused by this problematic pathogen, the difficult antimicrobial management and the high mortality associated with these infections, the Infection Section of the ESICM decided to develop clear recommendations carried out by expert opinion leaders. Our main objective is to provide clinicians clear and practical recommendations to optimize therapy and to establish the necessary control measures in order to eradicate *A. baumannii*. These recommendations are based on results of epidemiological and clinical studies and on expert opinions when no scientific evidence is available.

Methodology

To proceed with this project, experts were first asked if they were willing to participate. They were chosen on the basis of their expertise in the field of diagnosis and treatment of severe infections caused by *A. baumannii,* and in strategies to control *A. baumannii* outbreaks, and further on their experience in generating consensus documents. Clinical microbiologists with profound knowledge about this bacterium were also involved. Contact was made through the Chair of the Infection Section of the ESICM.

The searching criteria are detailed in the ESM. The coordinators of this project (J.G.M., M.B.) named by the Chair of the Infection Section of the ESICM, designed the methodology and the different topics to be included. This proposal was sent and approved by all the experts.

The writing committee (J.G.M., M.B., G.D., G.P.) wrote the first draft which was sent to the rest of the group for their critical review. A face-to face meeting was held in Barcelona (12 May 2014) in order to discuss the draft and the recommendations. Strength and quality of recommendations were graded in accordance with the ESCMID guidelines (Table 2 of the ESM). The items receiving more than 80 % agreement were approved. A second document was sent by e-mail to all the participants. All the experts of the panel agreed with the final document and with the recommendations. The terms and definitions used in this manuscript are explained in Table 3 of the ESM.

Microbiological issues

Identification of *A. baumannii* in clinical laboratories

The need for identification of *Acinetobacter* spp. to species level in routine clinical practice has long been debated. From a clinical and infection control perspective, however, it is mandatory to distinguish between the *A. baumannii* group and *Acinetobacter* spp. outside the *A. baumannii* group, since the latter organisms are only

occasionally causing human infections and are usually susceptible to a wide range of antimicrobials. Moreover, it is also important to identify the species within the *A. baumannii* group, since a higher overall mortality was observed in patients with *A. baumannii* bloodstream infection than in patients with bacteremias caused by *A. nosocomialis* and *A. pittii* [6]. In addition, carbapenem resistance is more frequently found in *A. baumannii*, and if these three species are not correctly identified, resistance rates for *A. baumannii* may be underestimated. Recently, the number of *A. pittii* isolates producing carbapenemases of different classes and hence resistant to carbapenems has been increasing worldwide [7, 8]. Identification to genus level of *Acinetobacter* spp. is straightforward in a microbiological laboratory. However, neither conventional microbiological methods nor semi-automated methods allow for reliable identification to species level. Many molecular methods have been developed and validated for the identification of *Acinetobacter* species [9].

In recent years, MALDI-TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) has been increasingly used for identification of microorganisms. It has been demonstrated that MALDI-TOF MS allows for accurate identification of species comprising the *A. baumannii* group [10]. The use of this technique as it becomes more widespread will finally solve the complex issue of identification of *Acinetobacter* to species level.

Recommendations

Clinical microbiology laboratories should distinguish between *Acinetobacter* spp. of the *A. baumannii* group (i.e., *A. baumannii*, *A. nosocomialis* and *A. pittii*) and *Acinetobacter* spp. outside the *A. baumannii* group (BII).

Identification of members of the *A. baumannii* group to species level is not mandatory in routine clinical microbiology laboratories (BII). This identification is, however, recommended for research purposes and outbreak analysis (BII).

MALDI-TOF MS is recommended for accurate phenotypic species identification of members of the *A. baumannii* group in clinical microbiology laboratories, obviating the need for using genotypic identification methods (BIII).

Detection of *A. baumannii* hetero-resistance by clinical microbiology laboratories

In 2006, Li et al. [11] first described colistin heteroresistance of *A. baumannii*, which was defined as the emergence of resistance to colistin by a subpopulation from an otherwise susceptible (MIC ≤2 mg/L) population. In addition, carbapenem heteroresistance has been reported [12]. Because heteroresistance detection requires a special method and equipment, most laboratories cannot routinely perform this test. The rate of heteroresistance among recent reports varied from 18.7 to 100 % [13–15]. Previous use of colistin might be a risk factor for higher rates of heteroresistance [16]. The detection of colistin heteroresistant *A. baumannii* in clinical isolates provides a strong warning that, if colistin is used inappropriately, there may be substantial potential for the rapid development of resistance and therapeutic failure. The clinical implications of heteroresistance are currently unknown.

Recommendations

Microdilution (standardized or commercial) cannot adequately detect the presence of heteroresistant populations in *A. baumannii*; however, the observation of colonies in the inhibition zones of a disc or an *E* test may be used as an indirect approach (CII).

Based on published data, it is premature to draw any conclusions regarding the clinical impact of heteroresistance (CIII).

Treatment of *Acinetobacter* infection

In critically ill patients with severe infection, when is it justified to cover *A. baumannii* and what empirical antimicrobial therapy is recommended?

Adequate empirical therapy of severe infections caused by *A. baumannii* is crucial in terms of survival [17, 18]. Due to the increasing antimicrobial resistance and the lack of well-designed studies, empirical treatment for *A. baumannii* infections often represents a challenge. Traditionally, carbapenems (except ertapenem that lacks activity against *A. baumannii*) have been the drug of choice for the empirical treatment of *A. baumannii* infections, and they are still the first-line agents for the empirical therapy in areas with high rates of susceptibility [19]. However, as mentioned previously, one of the distinguishing features of *A. baumannii* is its impressive propensity of acquiring antibiotic resistance which makes the selection of an appropriate empirical antimicrobial regimen extremely difficult [1].

Carbapenems may not be considered the treatment of choice in those areas with high rates of carbapenem-resistant *A. baumannii*. Nowadays, polymyxins are the antimicrobials with the greatest level of in vitro activity against *A. baumannii* [20–22]. However, their indiscriminate use may contribute to selection of further resistance and may also expose patients to unnecessary toxicity. Thus, selection of patients who should receive empirical treatment covering *A. baumannii* is essential. The most frequently reported risk factors for *A. baumannii*

infections in the ICU are shown in Table 1 [23, 24]. Several studies have reported a direct correlation between colonization pressure and the acquisition of this pathogen [25, 26]. In addition, previous colonization with *A. baumannii* resistant to carbapenems is a variable independently associated with the development of an infection caused by carbapenem-resistant (CR) *A. baumannii* [27]. Therefore, new infections occurring during an outbreak or in a previously colonized patient are the most compelling reasons for *A. baumannii* empirical coverage. The dosages of the different antimicrobial agents recommended by this panel are shown in Table 2.

Recommendation

A. baumannii empirical coverage is recommended in severe infections occurring during an *A. baumannii* outbreak, in endemic situations, or in a previously colonized patient (BIII).

Carbapenems are the drugs of choice for infections caused by *A. baumannii* in areas with low rates of carbapenem resistance (BII). Otherwise, carbapenems should not be used, at least in monotherapy, for severe infections in areas with a high rate of resistance to this group of antibiotics (CIII).

A polymyxin is suggested as part of the empirical treatment in patients with high suspicion of CR *A. baumannii* (CIII).

Other agents (i.e., tigecycline and sulbactam) should not be used, at least in monotherapy, for the empirical therapy (CIII).

What is the role of sulbactam in the management of severe *A. baumannii* infections? What dosage is recommended?

Sulbactam is a penicillanic acid sulfone which, as well as being a β-lactamases inhibitor, has intrinsic activity against *A. baumannii*. Unfortunately, a steady increase in sulbactam MIC in *A. baumannii* clinical isolates has been observed in the last decade [21]. Sulbactam is a drug with undetermined breakpoints for *Acinetobacter* spp. and there is no consensus on how to perform susceptibility testing. Susceptibility testing using semi-automated methods is unreliable but a MIC ≤4 mg/L as determined by the Etest is frequently accepted to indicate susceptibility [28]. A recent PK/PD study performed in healthy volunteers concluded that a 4-h infusion of 3 g of sulbactam every 8 h constitutes the best treatment option for isolates with a higher MIC of 8 mg/L [29].

In small series, clinical results using ampicillin-sulbactam to treat severe *A. baumannii* infections were similar to those obtained with imipenem [30–32]. Ampicillin-sulbactam was more effective than polymyxins in a retrospective study that included CR *Acinetobacter* infections of diverse origins but excluding urinary tract infections [33]. A randomized study evaluated the efficacy and safety of two sulbactam regimens in patients with VAP caused by multi-drug-resistant (MDR) *A. baumannii*. The clinical and bacteriological cure was similar with both regimens and with excellent tolerance [34]. This same group compared in 28 patients with MDR *A. baumannii* VAP, ampicillin-sulbactam (9 g every 8 h) with colistin (3 million IU every 8 h). Clinical and microbiological response was comparable in both groups. Nephrotoxicity was higher with the use of colisitin (33 vs. 15.3 %) although this difference did not achieve statistical significance [35]. Similarly, in a retrospective study which included 98 patients with CR *A. baumannii* VAP, clinical cure rates were similar in both groups, although microbiologic cure rates at day 7 were significantly lower in the colistin group. Impairment of renal function and 30-day mortality were also significantly higher in the colistin group [36]. In a large prospective study, Paul et al. concluded that colistin is less effective and more toxic than beta-lactam antibiotics (including ampicillin/sulbactam) in the treatment of severe infections caused by multiresistant Gram-negative bacilli (GNB), 55 % of them *A. baumannii* [37].

Table 1 Risk factors for development of *A. baumannii* infections in the ICU

Prior colonization with *A. baumannii*
Immunosuppression
Unscheduled admission
Respiratory failure at admission
Previous antimicrobial therapy
Previous sepsis in ICU
Multiple invasive procedures
Prior central venous or urinary catheterization, mechanical ventilation, and nasogastric tube
Previous use of carbapenems and 3rd generation cephalosporins
Older age
Long ICU stay

Adapted from references [1, 23, 24]

Recommendations

Sulbactam has intrinsic activity against *A. baumannii* and other *Acinetebacter* spp. and maybe a suitable alternative in the directed therapy for *A. baumannii* at a MIC ≤4 mg/L (CIII).

In strains susceptible to colistin and demonstrating a low MIC for sulbactam (≤4 mg/L), the use of sulbactam may be preferable in the directed therapy based on its better safety profile and to preserve colistin (CIII).

For severe infections, we recommend 9–12 g/day of sulbactam in 3 daily doses (BII).

Table 2 Recommended doses of antimicrobials for *A. baumannii* infections in patients with normal renal function

Antibiotic	Loading dose[a]	Daily dose	Observations
Imipenem[b]	Not required	0.5–1 g/6 h	Extended infusion is not possible due to drug instability High doses are associated with seizures
Meropenem[b]	Not required	2 g/8 h	Extended infusion (3–4 h) is recommended, In this case, first dose (2 g) should be administered in 30-min
Sulbactam[b]	Not required	9–12 g/day (in 3 or 4 doses)	4-h infusion is recommended
Polymyxin E[b] (Colistin)	6–9 million IU[c]	9 million IU/day in 2 or 3 doses	One million IU of colistin is equivalent to 80 mg of CMS. See text for doses on intermittent hemodyalisis and CRRT[d]
Polymyxin B	2–2.5 mg/kg	1.5–3 mg/kg/day in 2 doses.	Continuous infusion may be suitable. Same dose in patients on CRRT[d]
Tigecycline	100 mg	50 mg/12 h	May be adequate in secondary bacteremia for approved indications (abdominal infections and SSTI[e])
	200 mg	100 mg/12 h	For other sources including pneumonia and primary bloodstream infection (consider combination with another active antimicrobial). Without approval by regulatory agencies
Rifampicin	Not required	600 mg/day or 600 mg/12 h	Always in combination therapy
Fosfomycin[b]	Not required	12–24 g/day (in 3 or 4 doses)	Always in combination therapy

[a] The loading dose should be administered in all patients including those with renal dysfunction
[b] Dose adjustment is necessary in case of renal dysfunction
[c] *IU* International Units
[d] *CRRT* continuous renal replacement therapy
[e] *SSTI* skin and soft tissue infection

A 4-h infusion is suggested to optimize its PK/PD properties and may allow the treatment of infections involving strains with a MIC of 8 mg/L (B III).

What is the role of polymyxins in the management of severe *A. baumannii* infections? Should we use polymyxin B or polymyxin E (colistin)? What dosages are recommended?

Polymyxins are a group of polypeptide cationic antibiotics. Only polymyxin B and polymyxin E (colistin) are used in clinical practice. Colistin is administered in its inactive form colistimethate sodium (CMS). Several ways of reporting colistin doses are used which may cause errors (see Table 2) [38].

Over the last decade, our knowledge on the clinical pharmacokinetic of colistin has increased considerably. Several studies have pointed out that intravenous administration of CMS may lead to suboptimal plasma concentrations and is associated with higher mortality [39]. In 13 critically ill patients with VAP caused by GNB, colistin was undetectable in bronchoalveolar lavage (BAL) performed at 2 h after the start of the CMS infusion (2 million international units every 8 h) [40].

The need for a loading dose of colistin has been recently demonstrated. Plachouras et al. [41] described in 18 critically ill patients receiving 3 million international units (IU) of CMS every 8 h that plasma colistin concentrations were sub-optimal for 2–3 days before reaching steady state. The authors recommended a loading dose of 9 million IU and 4.5 million IU every 12 h because colistin displayed a half-life that was relatively long in relation to the dosing interval. The target of colistin should be based on MIC, site, and severity of infection. However, it can be difficult to obtain therapeutic levels for *A. baumannii* with MICs >1 mg/L [42].

The clinical efficacy and its tolerability have been confirmed in a series of critically ill patients with bacteremia or VAP caused by MDR-GNB [43]. Nevertheless, a loading dose of 6 million IU may be adequate to reach therapeutic levels in non-obese critically ill patients with MDR-VAP [44]. Another conflicting issue is the colistin dose in patients on continuous renal replacement therapy, because therapeutic levels are not achieved with a dosage regimen of 2 million IU CMS every 8 h. The authors recommend that CMS dosage should not be reduced for patients undergoing continuous venovenous hemodiafiltration (CVVHDF), but rather should be even higher than the dose used in patients with normal renal function [45]. Regarding dosage in patients on intermittent hemodialysis, 2 million IU CMS every 12 h seems to be necessary given the extensive removal of CMS and colistin by dialysis [41, 46].

The efficacy of colistin in severe infections caused by *A. baumannii* has been demonstrated in several retrospective and prospective series [36, 47–50]. These studies have evaluated colistin mostly in directed therapy, whereas the information about its use in empirical therapy is rather scarce.

Polymyxin B is available for intravenous administration and not as an inactive prodrug as occurs with colistin. Current PK findings for CMS/colistin cannot be extrapolated to polymyxin B, dosages of which should be calculated based on body weight, while the plasma concentration is not influenced by renal function [51, 52]. A loading dose is recommended to achieve optimal plasma levels of polymyxin B on the first day. For patients on

renal replacement therapy, dosage adjustments are not necessary. In addition, the incidence of renal failure seems to be lower with polymyxin B than with colistin [53, 54].

Recommendations

Colistin is suggested as part of the empirical treatment in patients with severe infections and high probability of CR *A. baumannii*, such as during outbreaks or in patients colonized with this pathogen (BIII).

For directed therapy, colistin should be preserved for treating infections produced by *A. baumannii* strains showing resistance to all beta-lactams, fluoroquinolones, tigecycline (only for approved indications) (BIII).

When using colistin and until more data are available, we recommend the use of a loading dose of 6–9 million IU and subsequently high, extended-interval maintenance doses (4.5 million IU/12 h) in critically ill patients and patients with severe sepsis/septic shock with creatinine clearance above 50 mL/min; the maintenance dose should be individually adjusted according to creatinine clearance (BII).

For patients undergoing continuous renal replacement therapy, even though the data are not consistent, a dose of at least 9 million IU/day is suggested (BIII).

For patients on intermittent hemodialysis, 2 million IU CMS every 12 h is recommended with a normal loading dose. Dialysis should be performed toward the end of a CMS dosage interval.

Polymyxin B may be a suitable alternative to colistin associated with less side effects. The recommended dose is 1.5–3 mg/kg/day; a loading dose of 2–2.5 mg/kg is suggested. For patients on continuous renal replacement therapy, dose adjustment is not necessary (BIII).

In patients with severe *A. baumannii* infections, does tigecycline constitute an alternative in the empirical and directed therapy? How should it be used?

Tigecycline is currently approved for the treatment of complicated skin and skin structure infections (cSSSIs) and complicated intra-abdominal infections (cIAIs) in adults. However, these infections are infrequently caused by *A. baumannii*.

A large ongoing multinational antimicrobial susceptibility database indicates that tigecycline inhibited 91.2/98.1 % (USA/European) of *A. baumannii* isolates at ≤2 mg/L, which is the susceptible breakpoint established by the FDA for Enterobacteriaceae [55]. In a recent European surveillance, 95.0 % of *A. baumannii* were inhibited by tigecycline at ≤2 μg/mL [56]. Of note, the susceptible breakpoint established by EUCAST for Enterobacteriaceae is ≤1 mg/L whereas no breakpoints for tigecycline have been established for *Acinetobacter* spp. by CLSI and by EUCAST.

The currently approved dosage is a 100-mg loading dose followed by a 50-mg dose administered twice daily. Tigecycline possesses a large distribution volume but Cmax in the serum does not exceed 0.87 mg/L with the standard regimen; treatment of intravascular/bacteremic infections by *A. baumannii* seems impossible with the approved regimen [57]. Clinical series confirm the poor outcome of patients with *A. baumannii* bacteremia treated with tigecycline [58].

In a randomized controlled phase 3 trial, tigecycline at the standard dose was compared with imipenem for the treatment of HAP [59]. In the clinically evaluable (CE) population, the cure rates in patients with VAP treated with tigecycline were lower than those in patients treated with imipenem (47.9 versus 70.1 %). A possible explanation was given from another PK study of three mechanically ventilated patients. At all three BAL sampling times, tigecycline concentrations in endothelial lining fluid (ELF) were very low (0.01–0.02 mg/l) [60].

In a double-blind randomized study of patients with VAP/HAP, two doses of tigecycline (150 mg followed by 75 mg every 12 h and 200 mg followed by 100 mg every 12 h) were compared to imipenem [61]. Numerically higher efficacy values were observed with the tigecycline 100 mg twice-daily dose (17/20; 85 %) compared to lower doses of tigecycline (16/23; 69.6 %) and imipenem (18/24; 75 %); however, *A. baumannii* was never identified as the etiologic pathogen.

Data on the clinical efficacy of tigecycline in real life for infections due to *A. baumannii* in critically ill patients derive mostly from retrospective non-comparative studies, usually with small numbers of patients, different infection localizations, and with diverse endpoints [62] [63–65]. More recently, the high dose regimen (loading dose 200 mg followed by 100 mg every 12 h) has been successfully and safely used in severe infections due to MDR bacteria (*A. baumannii* represented approximately one-third of the cases) [66]. Importantly, in these series, tigecycline was almost always administered in combination with other antimicrobials.

Recommendations

Tigecycline may be a suitable alternative in the directed therapy for infections of the approved indications (cSSSIs and cIAIs) caused by MDR *A. baumannii* if the MIC to this agent is ≤1 mg/L (BIII). In these infections, the currently approved regimen may be appropriate even for severe infections (BIII).

Tigecycline may be an option in the directed therapy for other infections (especially pulmonary infections) caused by *A. baumannii* if the tigecycline MIC is ≤1 mg/L and the isolate is resistant to other agents (BIII). In

these infections, the high dose regimen (loading dose 200 mg followed by 100 mg every 12 h) is suggested (BIII).

Due to the uncertainties about the efficacy of tigecycline in non-approved indications, we recommend its use in combination with another active agent, if possible (BIII).

In patients with severe *A. baumannii* infections, does the use of monotherapy or combination therapy impact on clinical outcome?

Experimental studies suggest that infections caused by carbapenem-resistant *A. baumannii* could be treated with a carbapenem in combination with another antibiotic (rifampicin or sulbactam) [67–69]. However, clinical experience has produced disappointing results [70, 71].

Synergy of colistin with diverse antibiotics such as imipenem, rifampin, fosfomycin, or tigecycline has also been shown in experimental models [72–74]. The combination of colistin plus rifampin has been evaluated in observational studies and clinical trials. Retrospective series concluded that this combination could be associated with a higher rate of clinical cure without apparent side effects [75–77]. Nevertheless, a randomized trial failed to demonstrate clinical superiority of the combination of colistin plus rifampicin over monotherapy with colistin in patients with severe infections (two-thirds with VAP) caused by extreme drug-resistant (XDR) *A. baumannii*, although microbiological eradication was significantly higher in the combination group [78]. The results were identical in another clinical trial that compared colistin plus rifampicin with colistin in patients with VAP caused by CR *A. baumannii* [79]. A recent systematic review has confirmed the lack of clinical efficacy using the combination of colistin plus rifampin in severe *A. baumannii* infections. Furthermore, rifampicin use was associated with a higher incidence of hepatotoxicity [80].

It is worth mentioning a retrospective study that compared monotherapy with colistin with patients that received combination therapy (colistin plus carbapenem, sulbactam, tigecycline or other agents) in XDR *A. baumannii* bacteremia. Rates of 14-day survival and microbiological eradication were significantly higher in the combination group but without differences in hospital mortality [81].

For patients with XDR *A. baumannii* pneumonia, a retrospective study has compared the use of colistin in combination with tigecycline, sulbactam or prolonged infusion of a carbapenem. The clinical success was similar in the three study groups, but unfortunately a control group treated with colistin in monotherapy was not included [82]. An observational study that included 101 patients with *A. baumannii* infection also failed to demonstrate clinical benefit of combination therapy after adjusting for confounding variables. Colistin plus tigecycline and a carbapenem plus tigecycline were the most frequently used combinations [83].

Several in vitro studies have documented the existence of an unforeseen potent synergism of the combination of colistin with anti-Gram-positive antibiotics with different mechanisms of action against carbapenem-resistant *A. baumannii* [84–87]. In a retrospective series, clinical benefit of the combination of colistin plus vancomycin was not documented in patients with *A. baumannii* VAP and bacteremia. In addition, the rate of renal failure was significantly higher in patients on combination therapy compared with those on monotherapy with colistin [88]. Conversely, a multicenter study that included a heterogeneous group of infections caused by different GNBs concluded that therapy with colistin plus a glycopeptide ≥5 days was a protective factor for 30-day mortality [89].

Fosfomycin is an "old" antibiotic that inhibits the first step of peptidoglycan synthesis and shows potent bactericidal action against many Gram-positive and Gram-negative bacteria. Although *A. baumannii* is intrinsically resistant to fosfomycin, a potent synergy of fosfomycin with colistin has been demonstrated in vitro. A recent open trial evaluated monotherapy with colistin compared to the combination of colistin plus fosfomycin. Microbiological response was higher in the combination group but without differences in clinical cure rate or mortality [90].

Finally, a systematic review concluded that, based on the results of the studies published up to the year 2013, no definitive recommendation can be done with regard to combination treatment or monotherapy for MDR, XDR, and pandrug-resistant (PDR) *Acinetobacter* infections [91]. Moreover, one potential benefit of combination therapy is prevention of the emergence of resistance under therapy (especially for colistin and tigecycline). This theoretic advantage has not been confirmed in a recent clinical trial [78].

Recommendations

There are no convincing data to recommend combination therapy in the directed therapy for *A. baumannii* infections (CIII). This recommendation is applicable for carbapenems, sulbactam, and colistin.

The routine combination of colistin plus rifampin in *A. baumannii* infections is not recommended (CIII).

The combination of colistin and an anti-Gram-positive agent (e.g., a glycopeptide, telavancin or daptomycin) in *A. baumannii* infections is discouraged (DIII).

The combination of sulbactam or a polymyxin with a second agent (tigecycline, rifampicin, or fosfomycin) may be considerd for clinical failures or for infections caused by an isolate with MIC in the upper limit of susceptibility (CIII).

In patients with severe *A. baumannii* infections, what is the optimal duration of treatment?

Treatment duration for infections caused by *A. baumannii* has been assessed in observational studies including predominantly VAP and bloodstream infections. In these studies, duration of treatment ranged from 10 to 22 days [92, 93].

In a meta-analysis of short versus prolonged antibiotic courses for the treatment of VAP, no difference was found in terms of mortality, recurrences and length of ICU stay [94]. However, a strong trend to lower relapse rates in the long-course treatment was observed. This was driven to a great extent by the study of Chastre et al. [95], who observed that patients with VAP due to non-fermenting Gram-negative bacilli, the majority of which belonged to *Pseudomonas* and *Acinetobacter* spp., had higher relapse rates.

It is obvious that trials focusing exclusively on *A. baumannii* infections and comparing different durations of antibiotics are lacking. Due to the paucity of data focusing on *A. baumannii* infections, the characteristics and properties of these pathogens as non-fermenting Gram-negative pathogens should be taken into consideration.

Recommendations

There are insufficient data to establish the optimal treatment duration in patients with *A. baumannii* infection. As with other pathogens, duration of therapy depends on infection localization (CIII).

Duration of treatment should be individualized. However, we suggest maintaining antimicrobial therapy for 2 weeks in patients with severe infections such as VAP or bacteremia, especially in those manifested as severe sepsis or septic shock. Shorter duration of therapy may be acceptable in patients with less severe infections (CIII).

Specific issues

In patients with A. baumannii pulmonary infections, what is the role of nebulized antibiotics?

Although diverse antibiotics have been nebulized, the most extensive experience in relation to *A. baumannii* VAP exists with aminoglycosides and colistin. The use of appropriate devices is essential to assure clinical and microbiological utility of nebulized antibiotics.

Available information derives from clinical studies that included MDR pathogens usually with a high predominance of *A. baumannii*. The use of aerosolized colistin for MDR GNB pneumonia increases cure rates and may be reasonably efficacious and safe [96–100]. Nevertheless, other studies have concluded that the use of aerosolized colistin in conjunction with intravenous colistin did not provide additional therapeutic benefit to patients with MDR VAP due to GNB [101]. Moreover, colistin failed to demonstrate a beneficial effect on clinical outcome in VAP caused by GNB [102]. In contrast, a retrospective case–control study has recently demonstrated a higher rate of clinical cure with nebulized colistin in microbiologically documented VAP caused by colistin-only susceptible Gram-negative bacteria (61.5 % were *A. baumannii*) [103]. Doses used in these studies have ranged from 2 to 6 million IU daily. Nevertheless, an observational study has reported a high clinical cure rate with a high dose of nebulized colistin (5 million IU every 8 h) delivered using a vibrating plate nebulizer either in monotherapy or combined with a 3-day intravenous aminoglycoside therapy [104].

Regarding aminoglycosides, several studies have evaluated tobramycin or amikacin with promising results in patients with MDR GNB VAP, especially when the drug is delivered using a vibrating nebulizer [105–107]. Systemic absorption of these antibiotics has been confirmed although trough serum concentrations remain below the renal toxicity threshold.

The efficacy of nebulized antibiotics on the microbiological eradication and clinical cure of patients with MDR *A. baumannii* tracheobronchitis is encouraging [99, 108]. However, optimal therapy for ventilator-associated tracheobronchitis is a matter of hot debate out of the scope of this document. Very few information exists about the use of nebulized antibiotics in cases of *A. baumannii* airway colonization and no definitive conclusion can be drawn especially due to the lack of a control group [109].

Recommendations

Nebulized antibiotics cannot be recommended routinely in the therapy of *A. baumannii* VAP. Nevertheless, we recommend the use of nebulized antibiotics in the following situations: treatment of patients who are nonresponsive to systemic antibiotics, recurrent VAP, or isolates with MICs close to the susceptibility breakpoint (BIII).

Nebulized antibiotics should be delivered using ultrasonic or vibrating plate nebulizers (AII).

The selection of colistin or an aminoglycoside should be done based on susceptibility results. For isolates that are susceptible to both aminoglycosides and colistin, no definitive recommendation on which antibiotic to choose can be given (CIII).

In patients with pneumonia, nebulized antibiotics should always be used in combination with intravenous antimicrobial therapy (BIII).

In patients with *A. baumannii* tracheobronchitis, we recommend the use of nebulized antibiotics, but further studies are needed to determine whether intravenous antimicrobial therapy is also necessary (CIII).

There are insufficient data to establish the optimal dose of nebulized colistin. We recommend 2 million IU every 8 or 12 h, although higher doses can be used in non-resolving cases (BIII).

Nebulized antibiotics should not be used in patients with *A. baumannii* colonization (DIII).

What is the recommended management of A. baumannii meningitis and ventriculitis?

Meropenem has been the drug of choice for nosocomial meningitis and ventriculitis to cover Gram-negative bacilli including *A. baumannii*. However, as in other infections, colistin is frequently the only available option, but its penetration into the cerebrospinal fluid is poor even in inflamed meninges [110]. A recent study showed that only the combination of parenteral with intrathecal (IT) or intraventricular (IVT) administration of colistin has the potential to achieve therapeutic concentrations and eradicate *A. baumannii* from the central nervous system (CNS) [111].

A successful clinical and bacteriological outcome of 89 % has been reported in 83 patients treated with IT or IVT colistin for *A. baumannii* CNS infections [112]. The median IT/IVT dosage used in adults was 125 000 IU with a wide range between 20 000 IU and 500 000 IU administered once or twice daily. The dose recommended by the Infectious Diseases Society of America is 125.000 IU once daily [113]. The need of a loading dose of 500.000 IU has recently been advocated [114].

CNS penetration of sulbactam ranges from <1 to 33 % depending on meningeal inflammation. Sulbactam may constitute a valid alternative for CR *A. baumannii* meningitis in isolates with low sulbactam MIC of ≤4 mg/L [115]. Regarding duration of treatment, no comparative trials exist. Actually, 21 days for treatment of Gram-negative meningitis is recommended. Three negative CNS cultures on separate days are required to decide on the end of IT/IVT treatment [114].

Recommendations

We recommend that empirical treatment of post-neurosurgical meningitis in patients at risk of *A. baumannii* infection should include high dose meropenem (2 g TID) plus colistin in areas with high rates of carbapenem resistance (BIII).

Dosing of intravenous colistin does not differ from doses used in other localizations (BIII).

We recommend adding IT/IVT colistin (dose 125.000–250.000 IU once daily) in episodes caused by MDR *A. baumannii* treated with intravenous colistin (BIII). No definitive recommendation can be made regarding the need of an IVT loading dose (BIII).

An aminoglycoside IT or IVT (daily does of 10–50 mg of amikacin or 5–20 mg of tobramycin) constitutes an alternative to colistin, if the strain is susceptible (BIII).

The optimal duration of treatment of *A. baumannii* meningitis/ventriculitis is unknown. However, we suggest continuing antimicrobial therapy for 3 weeks. Monitoring of cerebrospinal fluid sterilization can be of aid in tailoring the duration of therapy (BIII).

Prevention of *Acinetobacter* colonization/infection

One important feature of *A. baumannii* is its propensity to cause outbreaks and to become endemic. *A. baumannii* transmission is mainly due to interactions between healthcare providers, patients, and contaminated fomites in the environment. An in-depth review about transmission mechanisms is included in the ESM. This information is crucial to design strategies to control *A. baumannii* outbreaks and epidemics.

What strategies should be implemented to control an *A. baumannii* outbreak?

When cases of MDR, XDR or PDR *A. baumannii* first appear or are increasing, an epidemiologic investigation should be initiated. Introduction of a new resistance pattern also suggests transmission and deserves urgent investigation. Once a transmitted organism is endemically established, and irrespective of whether a common source could be eliminated, containment may require multifaceted interventions and, in most cases, aggressive and resource-demanding measures [116–118]. The most important components are the following (Fig. 1):

Infection control measures: Infection control interventions, cohort isolation, improved hand hygiene compliance, enhanced cleaning and environmental disinfection have been successful at reducing nosocomial infection rates and controlling outbreaks due to *A. baumannii* [119–122].

Hand hygiene is of paramount importance, because the majority of transmission events occur via the healthcare workers' hands [123, 124]. Single rooms are advisable; if single rooms with dedicated staff cannot be provided, cohorting of patients harboring the same organism is an alternative [125]. Cohorting of staff dealing only with colonized/infected patients may cause significant stress among healthcare workers and the administration.

The role of environmental cleaning in controlling *A. baumannii* has been described widely [126–129]. Therefore, environmental cleaning has been emphasized as one

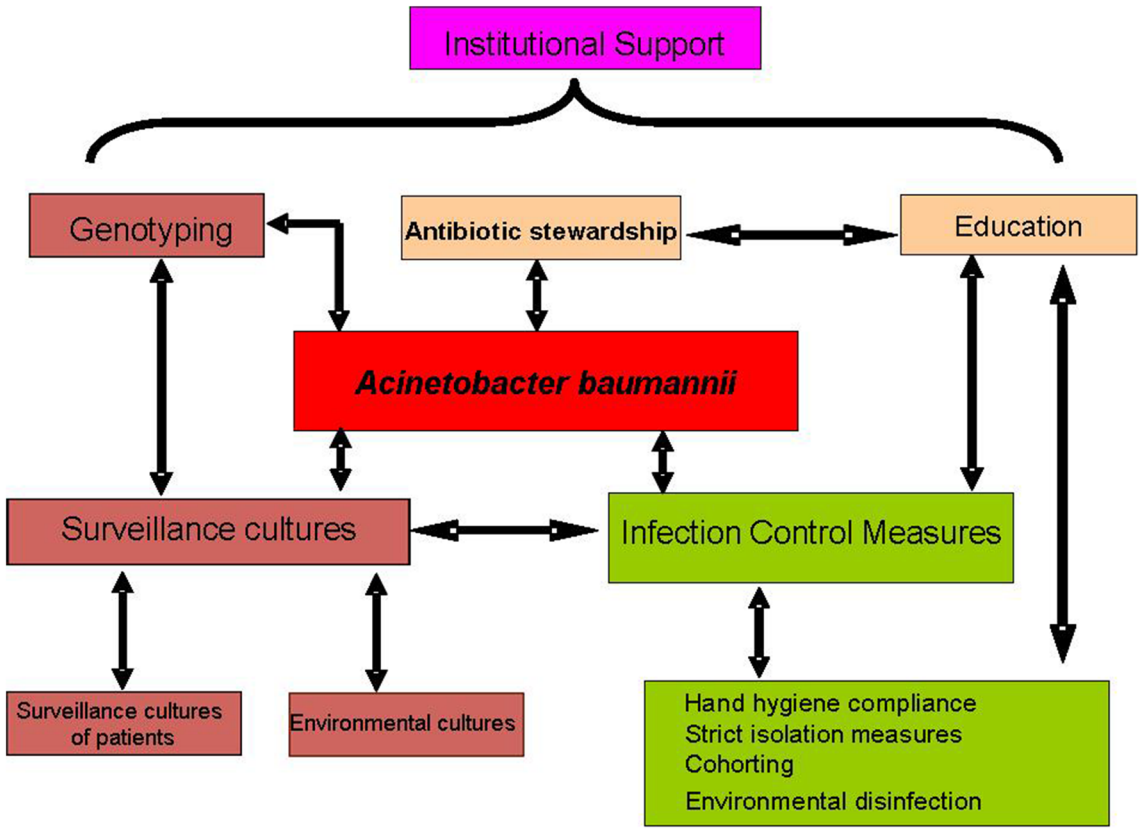

Fig. 1 Measures which should be necessary implemented to combat an *A. baumannii* outbreak

of the important components of an effective infection-control strategy [122, 130].

Surveillance cultures of patients: This intervention is commonly applied in outbreak situations, targeting patients involved in the outbreak or being at risk of transmission. Single site cultures (i.e., from nostrils) may have unacceptably low sensitivity (13–29 %); cultures drawn from six sites increased sensitivity to 50 % in one study [131]. Possible sites for surveillance cultures include: the nose, throat, skin sites such as the axilla and/or groin, the rectum, open wounds and endotracheal aspirates. A strategy of weekly pharyngeal and rectal swab cultures in 73 patients newly admitted to an ICU identified 46 (96 %) of the 48 patients who became colonized with A. *baumannii* [132]. The intervention requires a predefined protocol and collaboration with the laboratory. An approved plan should also exist in order to communicate the results rapidly and streamline appropriate infection control actions. A recent European guidelines strongly recommends the implementation of an active screening programme as well as contact precautions to reduce the spread of different GNB, including A *baumannii* [130].

Regarding culture media, chromogenic media are culture media that are designed for rapid and simple detection of bacteria. CHROMagar *Acinetobacter* (CHROMagar; Paris, France) is a chromogenic media recently developed for the rapid identification of MDR *A. baumannii*. It is an agar plate containing antimicrobial agents which inhibit the growth of most Gram-positive organisms as well as carbapenem-susceptible Gram-negative bacilli. In peri-anal swabs and stools, this selective media, compared with a molecular assay, exhibits a sensitivity and specificity of 91.7 and 89.6 %, respectively [133]. In peri-anal swabs and sputum of critically ill patients, this media detected 100 % of all *A. baumannii*, including MDR isolates [134].

Environmental cultures: This intervention is rational in outbreak situations or in endemic situations, when a source in the inanimate environment is suspected. A wide range of surfaces may be sampled, from equipment to wall surfaces and water supplies [1]. Again, a predefined protocol should be applied; resources may require specific transport containers or pre-moistened sponge sticks [135, 136]. In contrast, environmental cultures taken during outbreaks may also be repeatedly negative [137].

Genotyping of the isolates: See relevant section below.

Antibiotic stewardship: Antibiotic restriction policies are suggested as an additional intervention to reduce further selection of resistance in circulating *A. baumannii* strains [130].

Interventions targeting the environment: As much as 50 % of rooms were found contaminated after terminal cleaning, and novel technologic equipments are available to monitor cleaning procedures, e.g., fluorescent dye and ATP bioluminescence [138, 139]. Rigorous cleaning and disinfection protocols with special focus on the terminal cleaning of a hospital room decreased the risk of healthcare-associated infections in recent studies. Hypochlorite solutions have been reported effective in controlling outbreak situations [140]. A concentration of 0.5 % sodium hypochlorite eradicates *A. baumannii* but lower concentrations are only capable of reducing the bacterial load [141]. There are several emerging technologies under investigation that show promise for effective environmental decontamination [142, 143]. A major disadvantage of the UV systems is that they are able to disinfect only areas that have a direct line of sight with the apparatus. The major disadvantage of hydrogen peroxide systems is the time required to disinfect and release the room to a new patient.

Temporary closure of the affected ward terminated the outbreak in some reports [144, 145]. A rapid closure of the ICU for controlling an MDR *A. baumannii* outbreak has been demonstrated to be cost-effective [146].

Administrative support: The effort is a collaborative work that comprises multiple groups of the hospital employees. It has to be complemented with multiple educative initiatives in order to help the stakeholders accept the necessity of the measures, ensure that the working protocol is well understood and improve compliance; equally important is the feedback of the results [147].

Recommendations

We consider that a single patient colonized or infected with *A. baumannii* represents the potential for transmission to other patients. Consequently, the detection of a single case of *A. baumannii* in an area with no previously identified cases should prompt the implementation of infection control measures (BIII).

Contact precautions must be used for all patients identified as having *A. baumannii* infection or colonization (AII).

We recommend the use of alert codes to identify promptly patients already known to be colonized or infected by *A. baumannii* (AIII).

All aspects of room and medical equipment cleaning should be carefully examined, with a determination of how each item is to be cleaned and who is responsible for doing so (AII).

Solutions of hypochlorite (0.5 %) are recommended for room and surfaces cleaning (BIII).

In outbreaks, at least once a week all patients should be screened for harboring *A. baumannii*. Rectal and pharyngeal swabs as well as tracheal secretions in ventilated patients are the best options (BII).

For surveillance cultures, we recommend to use chromogenic media developed for the rapid identification of MDR *A. baumannii* (BII).

An antibiotic stewardship program is indispensable in the fight to control an *A. baumannii* outbreak (AII).

It is necessary to obtain an unequivocal support of the institution for these initiatives (AIII).

How to cope with an endemic situation?

In some hospital settings, *A. baumannii* has become endemic, a situation which is much more difficult to control than an outbreak [27, 148–150]. Nevertheless, the epidemiology of *A. baumannii* infections is complex with the conversion of an outbreak to an endemic situation or the coexistence of epidemic and endemic infections [151].

The development of an endemic situation is clearly favored by the selection pressure of antimicrobials. Moreover, environmental contamination has a recognized role in the transmission of A. *baumannii [*152]. In endemic situations, most epidemiological surveys have demonstrated the predominance of one or a few hospital-specific endemic clones [153, 154].

Infection control measures implemented in endemic situations are costly, but several studies have provided examples about the long-term efficacy of an active multifaceted strategy to control these situations [147, 155]. All these initiatives include active surveillance cultures, environmental cleaning and strict contact precautions to prevent transmission of *A. baumannii*. It is likely that any of these measures may not work separately, but the implementation of a "bundle" is the best approach to reverse this situation. As in outbreaks, the institutional and administrative support is of paramount importance for the success of these initiatives. It is very important to monitor the adherence of all the staff to the infection control measures. Moreover, education is essential to convince all the personnel about the epidemiological importance of MDR A. *baumannii* [130].

Recommendations

We recommend the implementation of a multifaceted intervention that includes reinforcement of education, antibiotic stewardship program, emphasis on hand hygiene, strict contact and isolation precautions, environmental cleaning and targeted active surveillance in an attempt to eliminate endemic *A. baumannii* (AII).

This programme should have the institutional and administrative support and should be maintained up to the control of the endemic situation (AII).

In an endemic situation, we recommend the implementation of an active screening at ICU admission with pre-emptive contact precautions when a patient is admitted to the ICU that should be maintained until confirmation of a negative result (BIII).

What are the indications for genotyping as a resource to fight againts *A. baumannii*?

Genotyping is a microbiological method that allows determining strain relatedness and following transmission pathways to guide infection control measures and continuing efforts to eradicate/eliminate *A. baumannii*. Different genotyping approaches have been adopted for *A. baumannii*, in order to describe the characteristics and the kinetics of this spread, in an effort to also identify clues for its containment (see ESM for further details and recommendations).

Compliance with ethical standards

Conflicts of interest JGM serves on scientific advisory board for Pfizer and declares speaker honoraria from Pfizer, Gilead Sciences, Astellas Pharma and MSD. JGM has received scientific unrestricted grants from Astellas Pharma. HS declares financial relationships with Astellas, AstraZeneca, Basilea, Cubist, Durata, FabPharma, Gilead, MSD, Novartis, Pfizer, Roche, Tetraphase, The Medicines Company and Theravance. MA declares travel and speaker honoraria from Merck, Pfizer, Astellas, Gilead Sciences and Cubist. JMC declares has received travels and honoraria as speaker from Astellas Pharma, Novartis, Pfizer, MSD and Astra-Zeneca. JDW declares consultancy for Acelity, AtoxBio, Bayer Healthcare, Cubist, Smith&Nephew, Sumitomo Pharmaceuticals. NP has served on scientific advisory boards for MSD, Pfizer, Cepheid; has received funding for travel or speaker honoraria from MSD, Novartis, Gilead, Pfizer, Zambon, Angelini, Achaogen, Johnson & Johnson. JFT serves on scientific advisory board for Bayer, Merck, 3 M. JFT received scientific unrestricted grants from Merck, Astellas, 3 M, Pfizer. JFT declares travel or speaker honoraria from Merck, Gilead, Astellas, 3 M, Bayer. NP has served on scientific advisory boards for MSD, Pfizer, Cepheid, The Medicines Company; has received funding for travel or speaker honoraria from MSD, Novartis, Gilead, Pfizer, Zambon, Angelini, Achaogen, Johnson & Johnson, Astellas, Carefusion. JRZ declares travels and honoraria as speaker from MSD and Pfizer. MB serves on scientific advisory boards for AstraZeneca, Bayer, Cubist, Pfizer Inc, MSD, Tetraphase and Astellas Pharma Inc, funding for travel or speaker honoraria from Algorithm, Angelini, Astellas Pharma Inc., AstraZeneca, Cubist, Pfizer MSD, Gilead Sciences, Novartis, Ranbaxy, Teva. The other authors have not declared any conflict of interest regarding this manuscript.

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