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Monitoring and Management of Infections Caused by Acinetobacter baumannii

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Abstract
Background: Acinetobacter baumannii is a frequent cause of infections in hospitals around the world, which is very difficult to control and treat. It is particularly prevalent in intensive-care units (ICUs).
Methods: Literatures associated with the Acinetobacter baumannii group were identified and selected from PubMed databases and relevant journals.
Results: Acinetobacter genospecies 3 and 13TU possess a certain proportion in clinical isolates. There were considerable differences in epidemiologic features, clinical manifestations,antimicrobial resistances and therapeutic options among the Acinetobacter baumannii group. Compared with Acinetobacter genomospecies 3 and 13TU, Acinetobacter baumannii with a higher resistance to antimicrobial agents are easier to be treated inappropriately, and present a worse outcome in patients.
Conclusion: The increasing incidence of multi- and extensively drug-resistant Acinetobacter baumannii emphasizes the importance of administration of an adequate antibiotic strategy and the implementation of strict monitoring of the measures for controlling nosocomial infections.

Keywords: Acinetobacter baumannii; Acinetobacter genomospecies 3; Acinetobacter genomospecies 13TU; Antibiotic resistance, Nosocomial infections.

Introduction:

Acinetobacter baumannii is a Gram-negative, nonfermentative, obligate aerobic, coccobacilli that have a ubiquitous distribution in nature being recovered from soil or water, human skin, and respiratory tract[1,2]. Acinetobacter baumannii is an important nosocomial pathogen, with a rising prevalence of about 89.2% among hospitalized patients, especially in Intensive Care Unit (ICU) patients[3]. Antimicrobial treatment of these infections may be compromised by the multiple-drug resistance of many strains to Beta-lactams, aminoglycosides, and fluoroquinolones[4]. This bacterium causes a variety of diseases including urinary tract infections, endocarditis, surgical site infections, pneumonia, septicemia, and meningitis[1,5]. Numerous strains of A. baumannii have recently emerged to be resistant against a wide spectrum of antibiotics, particularly beta-lactams, which have so far been among drug choices for treatment of A. baumannii infections. Consequently, treatment of these infections has encountered serious problems[2,6].
Acinetobacter comprising more than 40 genospecies[7], of which Acinetobacter baumannii (Acinetobacter genospecies 2), Acinetobacter genospecies 3 and Acinetobacter genospecies 13TU are clinically most relevant genospecies[8]. They are phenotypically indistinguishable by use of routine laboratory technologies, the term "Acinetobacter baumannii group" has therefore been proposed to refer to these genospecies[9].
Acinetobacter spp. is a common cause of ventilator-associated pneumonia and bacteraemia[10]. The frequency of A. baumannii nosocomial infections is increasing[11–15] a fact that may partly be attributed to the ability of these organisms to cause hospital and inter-

hospital outbreaks[16]. Mortality in critically ill patients with Acinetobacter infections, particularly in those with ventilator-associated pneumonia and bloodstream infections, is high[17–21].
In this review, we introduce the differences in epidemiologic features, clinical manifestations, antimicrobial resistances and therapeutic options among these three distinct clinical entities.

Epidemiology:
The prevalence of health care associated infections caused by Acinetobacter is increasing among patients in intensive care units (ICUs) and immunocompromised hosts[22-25]. The most common clinical condition associated with these microorganisms is hospital-acquired pneumonia (HAP), particularly for patients receiving mechanical ventilator assistance[26]. Among the three Acinetobacter species, A. baumannii is associated with a poorer outcome and higher rates of antimicrobial resistance[27]. The mortality rates for bacteremia caused by A. baumannii range from 29.8 to 58.6%[27-29]. It has been previously reported that non-ventilated patients with HAP (NVHAP) caused by nosocomial pathogens have a better outcome than those with ventilator-associated pneumonia (VAP)[30-32].
Patients with bacteremic NVHAP and VAP caused by A. baumannii had similar crude mortality rates, but on logistic regression analysis those receiving ventilator assistance had a significantly lower mortality. This may have been due to better airway protection, more intensive monitoring with earlier diagnosis and treatment in patients with VAP, greater innate susceptibility to infection in those with NVHAP and differences in the virulence of A. baumannii[33].
During the last decade, treatment of these infections has become critical, depending on the emergence of multidrug-resistant strains, which has been associated with infection of hospital equipment (respirators, air-conditioning swimming, equipment for diagnostic imaging, etc.)[34]. The emergence of resistance to carbapenems has limited the treatment to the use of polymyxins, which is considered as the main therapeutic option. However, it has been observed that although the resistance to polymyxins is very rare in isolated Acinetobacter, clinical efficacy in the treatment of infections is not always satisfactory. It has been found that the biofilm synthesis due to these bacteria on a plastic medium was stimulated by iron deficiency in surrounding conditions imposed by the iron chelator 2,2-dipyridyl (DIP)[35]. Hence, it was reported that the iron is needed for the biofilm mode of growth of A. baumannii[36].
The bacterium Acinetobacter baumannii is presumed to have extensive association with the thalassemia patients due to the fact that these individuals require a regular blood transfusion for their management. This aspect makes them vulnerable to acquire infections and also develop iron overload in their body, which may provide a likely environment for the bacteria to flourish[37,38]. The chances for the bacterial transmission are higher either from the contaminated equipment or the already infected blood[39–40]. The mortality, due to the septic shock as a result of blood infection, is one of the common observations in the cases of thalassemia[41].

Microbiological Diagnosis:
Selection of specimen depends on the site of infection. The main specimens like Sputum or Tracheal aspirate or pleural fluid in usually taken from the patients suffering from pneumonia.
The blood samples for the purpose of culture to diagnose bacteremia or septicemia or sepsis should be taken from the patients. The blood sample must be drawn by following the standardized approach for blood withdrawal. Specifically, the approach of venepuncture should be used after the sanitization of skin through alcohol swab. A tourniquet should be used during the process of blood withdrawal. A volume of 10ml blood must be taken from the patients through standardized blood withdrawal techniques.

Media, Reagents, and Kits:
(i) MacConkey, Blood agar, Eosin Methylene Blue agar and Chocolate agar media are routinely used for culture.
(ii) Blood agar medium differentiates the hemolytic and non-hemolytic bacteria. Iso-sensitest agar medium can be used for the determination of resistance pattern against different antibiotics groups.
(iii) Isolates can be identified by API 20 E kit (Biomerieux,USA)[42].
Identification of Bacterial Isolates: Isolates should be identified via standard microbiological techniques, like colony morphology, Gram's staining, sugar fermentation, motility, catalase and oxidase tests, and other standard recommended tests[43,44] should be used for phenotypic characterization. Clinical samples should be collected from the patients and cultured on 5% defibrinated sheep blood Colombia agar, Eosin Methylene Blue agar and Chocolate agar and should be incubated at 37°C for 24 hours. Identification of the microorganisms should be carried out using conventional methods. Automated systems like VITEK 2 automated system (bioMerieux Inc, Mercy L'etoil, Fransa) can also be used for the identification of the bacterial isolates. For definitive identification of isolates to the species level, molecular methods can be used in the next step.
Molecular method:
Different molecular methods are available for the identification of Acinetobacter to the species level. The isolates can be identified to the species level using species-specific rpoB gene-based PCR as previously described[45]. In brief, a 350-bp fragment of the rpoB gene can be amplified from an isolate using two primers of 696F (50- TAY CGY AAA GAY TTG AAA GAA G-30) and 1093R (50- CMA CAC CYT TGT TMC CRT CA-30).
To investigate the heterogeneity of A. baumannii isolates, restriction fragment length polymorphism (RFLP) can be performed as described by other investigators, using TagI and HaeIII restriction endonucleases[46].
Antimicrobial Susceptibility Testing: Antibiotic sensitivity testing can be performed manually using disc diffusion method or through automated systems like VITEK 2 AST-N090 (bioMerieux Inc, Mercy L'etoil, Fransa) for amikacin, amoxicillin-clavulanate, cefepime, ciprofloxacin, colistin, gentamicin, imipenem, meropenem, piperacillin-tazobactam, tetracycline, tigecycline and trimethoprim-sulfamethoxazole. Outcomes should be interpreted according to CLSI (The Clinical and Laboratory Standards Institute) standards[47].

Management and antimicrobial resistance:
The management of A. baumannii infections can be difficult, due to the increasing number of isolates exhibiting resistance to multiple classes of antibacterial agents[5,6]. Agents potentially effective against A. baumannii include carbapenems, aminoglycosides (amikacin or gentamicin), tetracyclines (minocycline or doxycycline) and sulbactam[1,48–51]. However, combined resistance to all of the above agents is increasingly being reported[52–58]. Still, extensively resistant A. baumannii strains remain generally susceptible to polymyxins (colistin and polymyxin B), a fact that has contributed to the reconsideration and re-introduction of this practically abandoned for decades class of antibacterial agents into clinical practice[53,59]. Yet, the increasing use of polymyxins has the potential to lead to development of bacterial resistance against these agents[60,61].
The main danger associated with A. baumannii is its capability to acquire antimicrobial resistance genes extremeles rapidly, leading to multidrug resistance[62]. The antibiotic resistance is especially common in ICUs, an environment with a high antibiotic pressure and severly ill patients[63]. Antimicrobial resistance among Acinetobacter spp. has increased substantially in the past decade and has created a major public health dilemma. The emergence of multidrug resistant gram-negative bacilli and no new development of antibiotics has brought polymixins, back to use during the past few years, as the last resort for the treatment of infections caused by multi-resistant gram-negative bacteria[64,65].

Acinetobacter baumannii resistance to multiple antibiotics has left colistin (polymixin E), the drug abandoned in 1980s due to its unacceptable rates of nephrotoxicity, often as the only effective therapeutic option[64]. Unfortunately, resistance to colistin in A. baumannii (extensively drug-resistant A. baumannii) has been reported recently all over the world, with resistance rates ranging from <7% in most reports to 30.6% and 40.7% in reports from Korea and Spain, respectively[64]. The increasing incidence of multi- and extensively drug-resistant Acinetobacter spp. emphasizes the importance of administration of an adequate antibiotic strategy and the need for new and effective treatment options, as well as the implementation of strict monitoring of the measures for controlling nosocomial infections.

Discussion:
Although phenotypical differences could not be easily recognized in Acinetobacter baumannii, Acinetobacter genomospecies 3 and 13TU, they still had some differences in epidemiologic features, clinical manifestations, antimicrobial resistances and therapeutic options as demonstrated above. It could be concluded that Acinetobacter baumannii should be expressed as three clinical entities, and their clinic values were not equal. Compared with Acinetobacter genomospecies 3 and 13TU, the patients infected with Acinetobacter baumannii demonstrated greater antimicrobial resistances, and thus were more likely to receive inappropriate therapies. These findings emphasized the necessity of genospecies for better understanding the pathogenesis and epidemiology of infections caused by Acinetobacter baumannii. At the same time, the epidemiology and susceptibility of Acinetobacter baumannii may vary widely from hospital to hospital, surveillance of antimicrobial resistance and accurate identification of genospecies are important for physicians to develop appropriate therapies in treating patients with such infections. Multidrug resistant (MDR) A. baumannii is an opportunistic pathogen developing especially in the intensive care settings leading to infections such as bacteremia, nosocomial pneumonia, VAP, meningitis, CAUTI, central venous CRBSI and wound infection. Incidence of A. baumannii infections have increased in a number of regions in the world in the last decade and have caused to epidemics depending on the ability of this organism. In general, antibiotics effective against A. baumannii infections are carbapenems, polymyxins, sulbactam, tigecycline, and aminoglycosides[66,67]. A. baumannii is the most commonly isolated from the respiratory tract, blood culture, wound and urine samples[68]. That patients hospitalized in ICU mostly received wide spectrum antibiotic treatment leads to isolation of A. baumannii strains frequently from these units[69]. It is reported to be the most commonly isolated agent in Reanimation ICU[70]. The most important problem in treatment of A. baumannii infections is the increase of isolated strains resistant against multiple drugs together with the narrowing of the options in antibiotics to be used in the treatment. Carbapenem resistance rates are increasing to such an extent to threaten the world and this situation is gradually becoming a routine phenotype for the microorganism. Therefore, in order to take the microorganism under control, infection control strategies must be focused on besides the treatment options[71].

It is inevitable for clinicians to develop a road map about the approaches to resistant Acinetobacter infections, including trainings on the infection control and proper antibiotic use based on the antibiotic sensitivity status in their regions. We believe that this approach will reduce the rates of resistant infections.

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