Review Article

# The *Acinetobacter baumannii* group: a systemic review

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**BACKGROUND:** The *Acinetobacter baumannii* group, including *Acinetobacter baumannii*, Acinetobacter genomospecies 3 and 13TU, is phenotypically indistinguishable and uniformly identified as *Acinetobacter baumannii* by laboratories of clinical microbiology. This review aimed to demonstrate the differences among them.

**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 *Acinetobacter baumannii* group comprises three distinct clinical entities, and their clinical value are not equal.

**KEY WORDS:** *Acinetobacter baumannii*; Acinetobacter genomospecies 3; Acinetobacter genomospecies 13TU; Difference

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## INTRODUCTION

The genus Acinetobacter currently consists of more than 40 genospecies,[1] of which *Acinetobacter baumannii* (Acinetobacter genospecies 2), Acinetobacter genospecies 3 and Acinetobacter genospecies 13TU are clinically most relevant genospecies.[2] They are phenotypically indistinguishable by use of routine laboratory technologies, the term "*Acinetobacter baumannii* group" has therefore been proposed to refer to these genospecies.[3]

In clinical microbiology laboratories, simple and reliable methods are barely available to complete the identification of the *Acinetobacter baumannii* group. Besides that DNA-DNA hybridization is regarded as the gold standard, other molecular typing methods also have been developed and validated. It is recommended that amplified 16S rRNA gene restriction analysis (ARDRA)[4] and amplified fragment length polymorphism (AFLP)[5] are the most widely accepted methods. However, they are too laborious and far from being suitable for day-to-day diagnostic microbiology. In fact, *Acinetobacter baumannii*, Acinetobacter genospecies 3 and Acinetobacter genospecies 13TU are uniformly identified as *Acinetobacter baumannii* by the most widely used identification systems.[3,6] In this review, we introduce the differences in epidemiologic features, clinical manifestations, antimicrobial resistances and therapeutic options among these three distinct clinical entities.

## METHODS

Literatures associated with the *Acinetobacter baumannii* group were identified and selected from

PubMed databases and relevant journals.

# RESULTS

## Differences in epidemiologic features

Few clinical centers have completed the identification of clinical isolates of the *Acinetobacter baumannii* group (Table 1). It is obvious that just as *Acinetobacter baumannii*, Acinetobacter genospecies 3 and 13TU are also important nosocomial pathogens and possess a certain proportion in clinical isolates. Isolates belonging to Acinetobacter genospecies 3 and 13TU were also involved in a number of outbreaks in ICUs.[7–15] With the development of much more novel and accurate typing methodologies, an increase in infections caused by Acinetobacter genospecies 3 and 13TU might be observed in the future.

The genospecies of clinical isolates of the *Acinetobacter baumannii* group may vary considerably. In most regions, the *Acinetobactor baumannii* group was the most frequently isolated genospecies. But in Ireland[11] and Germany[16], Acinetobacter genospecies 3 was found to be the most predominant genospecies. In addition, the proportions of *Acinetobacter baumannii* and Acinetobacter genospecies 3 were approximately equal in the Netherland,[17] and Acinetobacter genospecies 13TU was the most prevalent genospecies in Norwegian blood cultures.[18] It is a pity that by far there is no such report about the genospecies identification of the *Acinetobacter baumannii* group in the mainland of China, further studies are needed.

## Differences in clinical manifestations

Ni et al[19] found that *Acinetobacter baumannii* preferably colonized or infected the respiratory tract, and such infections tend to occur in debilitated patients especially in the ICU. In comparison, Acinetobacter genomospecies 3 was more frequently involved in skin and soft tissue infections, such as surgical wound infection, and usually occurred in conventional wards, not in ICUs. Another study[20] comparing the bacteremic nosocomial pneumonia caused by *Acinetobacter baumannii* and Acinetobacter genospecies 13TU found that patients with *Acinetobacter baumannii* pneumonia were more likely to have abnormal hematological findings, lobar pneumonia and significantly higher APACHE II scores than those with Acinetobacter genospecies 13TU pneumonia. It seemed that different genospecies would lead to different clinical manifestations among the *Acinetobacter baumannii* group.

Studies comparing the different clinical manifestations of the *Acinetobacter baumannii* group infections concentrated on the bloodstream infections. These studies confirmed that patients with *Acinetobacter baumannii* bacteremia were associated with a higher 14-day or 30-day mortality rate and an in-hospital mortality rate than those patients with bacteremia because of Acinetobacter genospecies 3 or 13TU.[21,22] Patients with Acinetobacter genospecies 3 bacteremia and those with Acinetobacter genospecies 13TU had similar clinical features and outcomes.[23,24] Multivariate analysis revealed that bacteremia caused by *Acinetobacter baumannii* was one of the independent factors associated with the all-cause mortality.[20–23]

Patients with *Acinetobacter baumannii* bacteremia were more likely to have pneumonia, whereas those with bacteremia due to genospecies 13TU were more likely to have primary bacteremia.[22,24] The Charlson Comorbidity Index was also significantly different in bloodstream infections of the *Acinetobacter baumannii* group. Patients with Acinetobacter genospecies 3 and 13TU bacteremia had obviously higher Charlson scores than patients with *Acinetobacter baumannii* bacteremia. They were implicated in more concurrent diseases, especially malignancy, and more metastatic malignancies were seen in patients with Acinetobacter genospecies 3 bacteremia.[21–23] This may indicate a predilection of Acinetobacter genospecies 3 and 13TU in patients with malignancy. However, respiratory diseases such as COPD, pneumonia and mechanical ventilation were more prevalent in patients with *Acinetobacter baumannii* bacteremia.[14,22–24] Multivariate analysis also found that total parenteral nutrition (TPN) was used more frequently and a longer timeframe in the treatment of TPN before the onset of bacteremia in patients with *Acinetobacter baumannii* bacteremia, who had received TPN for about 15 days before the onset of bacteremia.[14,25] In addition, the duration from admission to the onset of bacteremia was a mean of 10 days longer in patients with

**Table 1.** The distribution of the *Acinetobacter baumannii* group in clinical isolates

| Region | *A. baumannii* group | *A. baumannii* (%) | Genospecies 3 (%) | Genospecies 13TU (%) |
|---|---|---|---|---|
| Ireland[11] | 72 | 25 (34.7) | 45 (62.5) | 2 (2.8) |
| Singapore[12] | 193 | 152 (78.7) | 18 (9.3) | 23 (11.9) |
| Korea[13] | 240 | 127 (52.9) | 15 (6.3) | 98 (40.8) |
| USA[14] | 271 | 187 (69.0) | 23 (8.5) | 61 (22.5) |
| Taiwan[15] | 1039 | 439 (42.3) | 133 (12.8) | 467 (44.9) |
| Germany[16] | 1741 | 335 (19.2) | 1053 (60.5) | 353 (20.3) |

*Acinetobacter baumannii* than in those with bacteremia because of Acinetobacter genospecies 3 and 13TU.[14,21]

It is clear that different genospecies of the *Acinetobacter baumannii* group are not equal clinically. From a clinical and infection control point of view, identifying the *Acinetobacter baumannii* group to species level is necessary, and it indicates clinical significance.

## Differences in antimicrobial resistances: mechanisms and sensitivities

The genus Acinetobacter has a propensity of rapidly acquiring resistance genes due to selective antimicrobial pressure and there are intrinsic resistance mechanisms typical to this genus, both of which lead to the high rates of resistance to multiple antimicrobial agents.[3] The mechanisms of antimicrobial resistance for genus Acinetobacter are shown in Table 2.

Studies also found that the antimicrobial resistance mechanisms were distinct for the *Acinetobacter baumannii* group. As for resistance to carbapenems, the blaIMP and blaVIM genes belonging to class B metallo-β-lactamase genes were more commonly found in Acinetobacter genospecies 3 and 13TU, whereas the class D carbapenemase genes were observed more often in *Acinetobacter baumannii*,[26,27] to which the blaOXA-51 gene was intrinsic.[28] For genes encoding aminoglycoside-modifying enzymes, *Acinetobacter baumannii* carried armA and aph(3')-Ia, whereas Acinetobacter genospecies 13TU possessed aph (3')-VI.[29] Moreover, *Acinetobacter baumannii* resistant to fluoroquinolones all contained a Ser83Leu substitution in the gyrA gene, but most of Acinetobacter genomospecies 3 and 13TU were fluoroquinolones susceptible and contained a wild-type Ser83 in gyrA.[30,31] Furthermore, the presence of RND-type efflux systems was likely species-specific. Because AdeABC and AdeIJK efflux transporters were highly specific to *Acinetobacter baumannii*, AdeDE and AdeXYZ were predominant in Acinetobacter genomospecies 3.[32,33] In addition, a study[34] investigated the different capacities of the *Acinetobacter baumannii* group to form biofilm at the air-liquid interface, which was almost 4 times higher for *Acinetobacter baumannii* and Acinetobacter genospecies 13TU than Acinetobacter genomospecies 3.

The differences in antimicrobial resistance mechanisms as mentioned above were associated with various antimicrobial resistances among *Acinetobacter baumannii*, Acinetobacter genospecies 3 and 13TU. Although a considerable increase of resistance to almost all antimicrobial agents was noted in the *Acinetobacter baumannii* group globally,[35,36] Acinetobacter genomoespecies 3 and 13TU remained susceptible to the majority of antimicrobial agents.[36] It was generally observed that *Acinetobacter baumannii* isolates had significantly higher resistance rates than the other two genospecies in most antimicrobial tests which even including carbapenems and tigecycline.[24] At the same time, the proportions of multidrug resistant strains and carbapenems resistant strains were also significantly higher in *Acinetobacter baumannii* isolates than Acinetobacter genomoespecies 3 and 13TU.[12,24,36] However, it should be noted that Acinetobacter genomoespecies 3 and 13TU isolates were less susceptible to polymyxin *E* (*colistin*) than *Acinetobacter baumannii*.[15,24,36] In addition, special

**Table 2.** The mechanism of antimicrobial resistance of Acinetobacter baumannii:[3]

| Resistance mechanisms | Antimicrobial agents |
|---|---|
| Produce antibiotics inactivated enzyme | |
| β-lactamas | β-lactams |
| Class A: extended-spectrum-β-lactamases (ESBLs): TEM, PER type | |
| Class B: the metallo-lactamases (MBLs): IMP, VIM, SIM type | |
| Class C: AmpC cephalosporinases | |
| Class D: serine carbapenemases (OXA type) | |
| Aminoglycoside-modifying enzymes (AMEs): APHs, AACs | Aminoglycosides |
| Alter the action sites of antibiotics | |
| Topoisomerase mutations in the genes gyrA and parC | Quinolones |
| Ribosomal (16S rRNA) methylation: armA | Aminoglycosides |
| Alteration in penicillin-binding proteins (PBPs) | β-lactams |
| Reduce the concentration of antibiotics in cells | |
| Decreased permeability of the outer membrane | Multidrug |
| Efflux pumps | |
| Plasmid-mediated transport protein: TetA, TetB, TetK | Tetracyclines |
| RND efflux systems: AdeABC, AdeDE, AdeXYZ, AdeIJK | Multidrug |
| Biofilm formation | Multidrug |

attentions should be paid to that the colistin and tigecycline resistance rates for Acinetobacter genomoespecies 13TU were up to about 20%.[15,36] Therefore, it must be emphasized that the emergence of pan drug resistant Acinetobacter genomoespecies 13TU might cause a great problem in the near future.

### Differences in therapeutic options

As *Acinetobacter baumannii* display resistance to more classes of antimicrobial agents than Acinetobacter genospecies 3 and 13TU, patients with *Acinetobacter baumannii* infections tend to be less likely to receive appropriate empirical therapy.[19,21,22,25] However, inappropriate antimicrobial therapy is just one of the factors independently associated with the mortality of patients with *Acinetobacter baumannii* infections.[37]

The drug resistance to *Acinetobacter baumannii* leaves extremely limited therapy options for physicians to treat the patients with carbapenems resistant (CR), multiple drug resistant (MDR), extensive drug resistant (XDR) and even pan drug resistant (PDR) *Acinetobacter baumannii* infections. The use of tigecycline or polymyxin E (colistin) alone for severe CR, MDR and XDR *Acinetobacter baumannii* infections seems not to be an optimal choice.[38] Case reports, case series and small comparative observational studies suggested that the combination antimicrobial therapies, such as the combination of colistin with rifampicin,[39,40] tigecycline and colistin,[40] were efficacious and demonstrated a lower-than-expected toxicity, but more clinical data obtained via controlled clinical trials were needed to confirm our preliminary conclusions. On the contrary, clinical isolates of Acinetobacter genomoespecies 3 and 13TU were usually susceptible to a range of antimicrobial agents, and it was much easier to treat the patients infected with Acinetobacter genomoespecies 3 or 13TU. The empirical antimicrobial agents including broad-spectrum-β-lactams and fluoroquinolones all displayed effective results.[41]

The CHINET 2011 surveillance of bacterial resistance in China also displayed that cefoperazone/sulbactam had a relatively lower resistance rate for the genus Acinetobacter isolates, of which 88.6% belonged to *Acinetobacter baumannii*.[42] When patients were considered to have been infected with *Acinetobacter baumannii*, without knowing the exact genospecies. Treatment was given with compound preparations containing sulbactam.[43] A dose of sulbactam 4.0 g/d was efficacious and safe.[38]

By now, studies on the differences in infections caused by *Acinetobacter baumannii* are rare, and more clinical data are needed to draw conclusions about the optimal therapies for each genospecies.

## 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.

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