

# Distribution and resistance of pathogens in liver transplant recipients with *Acinetobacter baumannii* infection

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**Background:** Drug-resistant *Acinetobacter baumannii* has become a major problem in liver transplant recipients. The aim of this study was to investigate the clinical presentation, distribution, and drug susceptibility characteristics in liver recipients with *A. baumannii* infection.

**Methods:** We retrospectively investigated 17 liver recipients who developed *A. baumannii* infection between January 1, 2007 and December 31, 2014. The distribution of *A. baumannii* and drug susceptibility characteristics were reviewed.

**Results:** Infectious complications due to *A. baumannii* appeared in 17 liver recipients, with a total of 24 episodes. Approximately 63% (15/24) of *A. baumannii* infections occurred within 2 weeks after transplantation. The most common source of infection was multiple culture-positive sites (35.3%, n=6), followed by the intra-abdominal/biliary tract (23.5%, n=4) and lung (23.5%, n=4). Eight patients (47.1%) had a body temperature of 38°C or higher at the onset of *A. baumannii* infection. Nine, seven, and 12 recipients had a serum creatinine level of >1.5 mg/dL, a white blood cell count of >15,000/mm<sup>3</sup>, and a platelet count of <50,000/mm<sup>3</sup>, respectively. There were five (29.4%) cases of septic shock and eight (47.1%) deaths. The rate of antibiotic resistance of *A. baumannii* to ten of 12 antibiotics investigated was more than 60%. Among the 24 infections caused by *A. baumannii*, 75% were carbapenem-resistant. The rods were relatively sensitive to tigecycline and cefoperazone-sulbactam.

**Conclusion:** The clinical manifestations of *A. baumannii* infection included a high body temperature, a decreased platelet count, an elevated white blood cell count, and onset in the early period after transplantation as well as high mortality. The antibiotic resistance rate of *A. baumannii* was extremely high. Prevention measures and combination antibiotic therapy are needed to improve the outcomes of liver recipients with *A. baumannii* infections.

**Keywords:** liver transplantation, *Acinetobacter baumannii*, infections, manifestation, drug resistance

## Introduction

Infection is still a leading contributor to patient morbidity and mortality in liver transplantation.<sup>1-3</sup> Approximately four episodes of bacterial infection during the first post-transplantation month were reported per patient per year in liver recipients.<sup>4</sup> A recent study reported that around 60% of liver recipients experienced early infection post-transplantation.<sup>5</sup>

*Acinetobacter baumannii* has emerged in recent years as a particularly problematic drug-resistant pathogen and can result in a wide range of infections, including bacteremia, pneumonia, urinary tract infection, and peritonitis. Previous studies demonstrated that 0.8%–15.9% of liver recipients developed *A. baumannii* bacteremia,<sup>6-15</sup> and Nie et al reported that 3.7% of liver recipients developed intra-abdominal infection

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caused by *A. baumannii*.<sup>16</sup> The overall mortality among liver recipients with *Acinetobacter* species infections ranged from 50% to 90%.<sup>14,15</sup>

Knowledge about *A. baumannii* infections is essential to improve global care for the liver transplant recipient. In this retrospective study, we investigated the clinical presentation, distribution, and drug susceptibility characteristics in liver recipients with *A. baumannii* infection.

## Materials and methods

We reviewed the medical records of 17 liver recipients diagnosed with *A. baumannii* infection between January 1, 2007 and December 31, 2014 at the Third Xiangya Hospital, Central South University, Changsha and Zhongnan Hospital, Wuhan University, Wuhan, both of which are university teaching hospitals in the People's Republic of China. We enrolled all patients with definite clinical signs of infection from whom *A. baumannii* were isolated from clinical samples. All subjects received dual drug immunosuppression comprising corticosteroids and cyclosporine or tacrolimus. Demographic, clinical, and laboratory records for these recipients were retrospectively analyzed. The laboratory variables comprised serum creatinine and albumin levels, and white blood cell, platelet, and lymphocyte counts, which were collected within the first 24 hours after the culture was drawn. The follow-up time of all liver recipients was 1 month after the onset of *A. baumannii* infection. The ethics committees of the two hospitals involved approved the study.

## Definition

A case was defined as a patient with *A. baumannii* infection according to the criteria established by the Centers for Disease Control and Prevention.<sup>17</sup> Nosocomial infection was defined as an infection that was absent during preadmission assessments but detected at least 48 hours after admission to the hospital.<sup>18</sup> Antibiotic therapy was considered appropriate if *A. baumannii* was susceptible in vitro to empiric antibiotics, which were administered within 48 hours of sampling for culture. Septic shock was diagnosed in recipients with *A. baumannii* infection who developed persistent dysfunction of at least one organ caused by hypoperfusion which was unresponsive to intravenous fluid challenge.<sup>19,20</sup> Mortality was defined as infection-related when death was associated with clinical signs of active *A. baumannii* infection without evidence of any other cause.<sup>21</sup>

## Microbiological examination

Specimens were taken from the liver recipients for routine bacterial culture and were immediately transported to the clinical microbiology laboratory. The Vitek-2 system (bioMérieux,

Marcy l'Etoile, France) was used to identify *A. baumannii*. Antibiotic susceptibility was determined by the Kirby-Bauer method and minimum inhibitory concentration tests according to guidelines established by the Clinical Laboratory Standards Institute.<sup>22</sup> *A. baumannii* with intermediate susceptibility to antibiotics was considered to be resistant. All 12 antibiotics used were commercially available products from Oxoid (Altrincham, UK), including aztreonam, piperacillin-tazobactam, cefoperazone-sulbactam, cefazolin, cefuroxime, ceftazidime, cefepime, amikacin, levofloxacin, meropenem, tigecycline, and trimethoprim-sulfamethoxazole.

## Results

Over the study period, 24 episodes of *A. baumannii* infection occurred in 17 liver recipients. Within 2 weeks of transplantation, there were 62.5% (15/24) episodes of *A. baumannii* infection. The median time taken to develop *A. baumannii* infection was 11.5 (interquartile range 5–20) days after liver transplantation. Positive cultures of *A. baumannii* were obtained from the lung (n=8), intra-abdominal/biliary duct (n=8), blood (n=7), and the urinary tract (n=1). Most episodes of infections were nosocomial (95.8%, n=23). Fifty percent (12/24) of all episodes of infection were related to inappropriate antibiotic therapy.

The mean age of the 17 liver recipients with *A. baumannii* infection was 49.7±8.6 years with a male predominance (64.7%, n=11). The most common sites of infection were multiple culture-positive (35.3%, n=6). Of these, one patient each occurred bacteremia accompanied by pneumonia and peritonitis, and bacteremia accompanied by urinary tract infection; two patients developed bacteremia accompanied by pneumonia; and two patients had bacteremia accompanied by peritonitis. Nine, seven, and 12 recipients has a serum creatinine level of >1.5 mg/dL, a white blood cell count of >15,000/mm<sup>3</sup>, and a platelet count of <50,000/mm<sup>3</sup>, respectively, at the onset of *A. baumannii* infection. About 24% of patients (4/17) had a serum albumin level of <35 g/L, and 17.6% (3/17) had a lymphocyte count of <0.5×10<sup>9</sup>/L. There were five (29.4%) episodes of septic shock and eight (47.1%) deaths. Eight patients (47.1%) had a body temperature of ≥38°C at the onset of *A. baumannii* infection. Table 1 shows the demographic, laboratory, and clinical characteristics of the 17 liver recipients with *A. baumannii* infection.

The antibiotic resistance rate of all *A. baumannii* infections to ten of 12 antibiotics investigated was more than 60%. Seventy-five percent of *A. baumannii* infections were carbapenem-resistant and ceftazidime-resistant, but were relatively sensitive to tigecycline (resistance rate 4.2%) and cefoperazone-sulbactam (resistance rate 45.8%). Rods

**Table 1** Demographic, laboratory, and clinical characteristics of 17 liver recipients with *Acinetobacter baumannii* infection

Characteristic	Value
Age, mean $\pm$ SD years	49.7 $\pm$ 8.6
Male sex, n (%)	11 (64.7)
Temperature $\geq$ 38°C, n (%)	8 (47.1)
Nosocomial origin, n (%)	16 (94.1)
Inappropriate antimicrobial use, n (%)	7 (41.2)
Septic shock, n (%)	5 (29.4)
Site of infection, n (%)	
Lung	4 (23.5)
Intra-abdominal/biliary tract	4 (23.5)
Blood	3 (17.6)
Multiple culture-positive sites	6 (35.3)
Time of infection onset, n (%)	
<2 weeks post-transplant	12 (70.6)
$\geq$ 2 weeks post-transplant	5 (29.4)
Induction therapy, n (%)	
Yes	1 (5.9)
No	16 (94.1)
Acute rejection prior to infection, n (%)	
Yes	1 (5.9)
No	16 (94.1)
Reoperation, n (%)	
Yes	4 (23.5)
No	13 (76.5)
Laboratory variables from blood, n (%)	
Platelet count <50,000/mm <sup>3</sup>	12 (70.6)
Lymphocyte count <300/mm <sup>3</sup>	3 (17.6)
Albumin <30 g/L	4 (23.5)
WBC count >15,000/mm <sup>3</sup>	7 (41.2)
Creatinine >1.5 mg/dL	9 (52.9)
Related mortality, n (%)	8 (47.1)

**Abbreviations:** SD, standard deviation; WBC, white blood cell.

were most resistant to cefazolin (resistance rate 87.5%) and cefuroxime (resistance rate 83.3%).

The drug resistance rate of *A. baumannii* was the highest in pneumonia and the rate of all *A. baumannii* infections to ten of the 12 antibiotics was  $\geq$ 75%. The drug resistance rate of *A. baumannii* causing bacteremia was the lowest and the rate

of all *A. baumannii* infections to seven of the 12 antibiotics was <50%. The antibiotic resistance rate of *A. baumannii* to the 12 antibiotics is shown in Table 2.

## Discussion

Infection is still one of the most important complications in liver transplantation. van Delden et al reported that the prevalence of multidrug-resistant *Acinetobacter* is increasing, and is related to higher rates of treatment failure in solid organ transplant recipients.<sup>23</sup> Shi et al reported that 62.5% of *A. baumannii* infections in bacteremic liver transplant recipients were multidrug-resistant rods.<sup>6</sup>

We found that the drug resistance rate of all *A. baumannii* infections to ten of the 12 antibiotics investigated was more than 60%. Drug susceptibility testing showed that *A. baumannii* was relatively susceptible to cefoperazone/sulbactam and tigecycline (drug resistance rate <50%). Seventy-five percent of *A. baumannii* infections were carbapenem-resistant in the present study, which is lower than the drug resistance rate of 82.4%–92.8% reported by previous studies targeting liver transplant recipients.<sup>12,14</sup> The study by Bodro et al<sup>24</sup> reported results similar to ours in solid organ transplant recipients with bacteremia. We also found that 75% of *A. baumannii* infections were ceftazidime-resistant, which is higher than the rate from a study suggesting that 50% of *A. baumannii* were ceftazidime-resistant.<sup>13</sup>

Most of the positive *A. baumannii* cultures were obtained from the lung (n=8) and intra-abdominal/biliary duct (n=8). Similarly, in a study of 37 liver transplant recipients, Kim et al reported the most common site of *Acinetobacter* infection to be the biliary tract (56.8%), followed by the pulmonary system (18.9%).<sup>14</sup> The reason for the lungs being common foci for *A. baumannii* infection is that *A. baumannii* can utilize short, fimbrial-like protrusions on the bacterial cell

**Table 2** Resistance of *Acinetobacter baumannii* to 12 antibiotics according to site of infection (n, %)

Antimicrobial drug	Blood (7)	Lung (8)	Intra-abdominal/biliary duct (8)	Urinary tract (1)	Cases of total drug resistance (n)
MEM	3 (42.9)	8 (100)	6 (75)	1 (100)	18 (75)
TZP	3 (42.9)	8 (100)	6 (75)	1 (100)	18 (75)
CAZ	4 (57.1)	7 (87.5)	6 (75)	1 (100)	18 (75)
FEP	3 (42.9)	8 (100)	6 (75)	1 (100)	18 (75)
CXM	4 (57.1)	8 (100)	7 (87.5)	1 (100)	20 (83.3)
CZO	5 (71.4)	8 (100)	7 (87.5)	1 (100)	21 (87.5)
AN	5 (71.4)	6 (75)	4 (50)	1 (100)	16 (66.7)
LVF	3 (42.9)	5 (62.5)	6 (75)	1 (100)	15 (62.5)
TGC	0 (0)	0 (0)	1 (12.5)	0 (0)	1 (4.2)
SXT	3 (42.9)	7 (87.5)	5 (62.5)	1 (100)	16 (66.7)
CFS	1 (14.3)	6 (75)	4 (50)	0 (0)	11 (45.8)
ATM	4 (57.1)	8 (100)	6 (75)	1 (100)	19 (79.2)

**Abbreviations:** MEM, meropenem; TZP, piperacillin-tazobactam; CAZ, ceftazidime; FEP, cefepime; CXM, cefuroxime; CZO, cefazolin; AN, amikacin; LVF, levofloxacin; TGC, tigecycline; SXT, trimethoprim-sulfamethoxazole; CFS, cefoperazone-sulbactam; ATM, aztreonam.

surface to attach with great avidity to bronchial epithelial cells.<sup>25,26</sup>

We also found the drug resistance rate of *A. baumannii* in pneumonia was higher than at other sites, in line with reports suggesting that extensively drug-resistant *A. baumannii* almost exclusively caused respiratory infections in solid organ transplant patients.<sup>27–29</sup>

Carbapenem-resistant *A. baumannii* infections are associated with a high mortality rate in solid organ transplant recipients.<sup>14,27,28,30</sup> The mortality in liver recipients with *A. baumannii* bacteremia can reach 100%.<sup>13</sup> In the present study, we found that liver recipients with *A. baumannii* infection had a high mortality rate of 47.1%. Our findings might be explained by the high proportion of nosocomial infections, the strong resistance of pathogens to commonly used antibiotics, and the high proportion of infections treated with inappropriate antibiotic therapy. Zhong et al also suggested that *Acinetobacter* sepsis led to fatal outcomes due to its multidrug resistance.<sup>31</sup>

The exceedingly resistant *A. baumannii* in liver transplant recipients poses a new therapeutic challenge. Recurrence or persistence of *A. baumannii* infection despite treatment with susceptible antibiotics has also been described.<sup>28,30,32</sup> Infections caused by carbapenem-resistant *A. baumannii* might be treated with cefoperazone-sulbactam and tigecycline according to our present findings. In immunocompetent patients with a sulbactam-susceptible *Acinetobacter* isolate, monotherapy with sulbactam was as effective as imipenem in the treatment of ventilator-associated pneumonia<sup>33</sup> and bloodstream infection.<sup>34</sup> Tigecycline, a glycylicycline derivative of tetracycline, has demonstrated success in the treatment of carbapenem-resistant *A. baumannii* infection.<sup>35</sup>

Monotherapy with an antibiotic has been reported to be associated with the emergence of resistant strains.<sup>36</sup> Combination therapy for multidrug-resistant bacteria may be beneficial.<sup>37</sup> One study reported a significantly higher survival rate in transplant recipients treated with a combination of colistin and carbapenem.<sup>28</sup> However, combination of colistin and tigecycline is associated with a high rate of treatment failure and emergence of resistance.<sup>38,39</sup> In addition, prevention measures are beneficial for liver recipients at high risk of infection. *A. baumannii* is a common isolate in the hospital environment.<sup>40</sup> *A. baumannii* infection can be caused by cross-infection. Therefore, some measures, such as limiting use of respiratory machines, early removal of unnecessary central venous catheters, and preventing cross-infection can effectively reduce the risk of *A. baumannii* infection. Active surveillance for *A. baumannii* is also recommended in institutions with high rates of resistant

*A. baumannii* to guide clinicians in their choice of effective perioperative prophylaxis in patients with suspected *A. baumannii* infection while the results of cultures are pending.

This study was limited by its retrospective design and small sample size. A further limitation was possible underestimation of *A. baumannii* infection because some cases received empiric courses of antimicrobial therapy before specimens for bacterial culture were obtained. Finally, this was a two-center study, so the external validity of our findings might be compromised.

## Conclusion

The clinical manifestations of *A. baumannii* infection included high body temperature, decreased serum albumin levels, low platelet and lymphocyte counts, elevated white blood cell counts, and onset in the early period after liver transplantation, as well as high mortality. The antibiotic resistance rate of *A. baumannii* was extremely high in liver recipients. To improve the outcomes of liver recipients with *A. baumannii* infection, prevention and combination antibiotic therapy can be beneficial.

## Disclosure

The authors report no conflicts of interest in this work.

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