Comparison of clinical characteristics and outcomes of bloodstream infections due to multidrug-resistant *Acinetobacter baumannii* and other Gram-negative bacteria in ICU patients

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Abstract

Background: Multidrug-resistant (MDR) bloodstream infection (BSI) by Gram-negative bacteria (GNB) is an important cause of mortality in the intensive care unit (ICU). The purpose of this study was to compare the clinical characteristics of some GNB BSIs and to analyze their drug resistance, with an emphasis on the analysis of prognostic risk factors related to MDR-Acinetobacter baumannii (A. baumannii) BSI.

Methods: A retrospective study was conducted in the ICU of lianyungang hospital in China. Patients with BSIs due to MDR-A. baumannii, MDR-Klebsiella pneumoniae (K. pneumoniae), MDR-Pseudomonas aeruginosa (P. aeruginosa) and MDR-Escherichia coli (E. coli) were included.

Results: The overall drug resistance rate to imipenem of A. baumannii and K. pneumoniae was significantly higher than that of P. aeruginosa and E. coli (95.8% and 75.5% vs 44.6% and 9.2% respectively). The mortality rates were 71.9%, 63.3%, 41.5% and 38.1%, respectively. The multivariate analysis of MDR-A. baumannii BSI, APACHE II score, hormone use, development of septic shock were associated with the 30-day mortality, while high albumin level with survival.

Conclusion: The treatment of MDR-A. baumannii and MDR-K. pneumoniae infection resulted difficult due to their high drug resistance rate. However, the understanding of the clinical characteristics of different BSIs might be helpful to predict, to some extent, the pathogenic bacteria involved so as to proceed with an early sensitive antibiotic treatment. The high mortality rate due to BSI MDR-A. baumannii might be correlated with APACHE II score, nutritional status, and hormone therapy, while septic shock was a warning sign of poor prognosis.

Background

Gram-negative bacteria (GNB) are very common pathogenic bacteria in the ICU [1–3]. Since the drug resistance rate continues to increase, it often causes refractory infections, among which the most serious is the bloodstream infection (BSI). Data from the China Antimicrobial Surveillance Network (CHINET) in 2018 (http://chinets.com/) show that the top four GNB causing BSIs are Escherichia coli (E. coli) (23.05%), Klebsiella pneumoniae (K. pneumoniae) (15.45%), Acinetobacter baumannii (A. baumannii) (3.2%) and Pseudomonas aeruginosa (P. aeruginosa) (2.9%). BSIs from these bacteria often occur in severe patients due to a frequent exposure to broad-spectrum antibiotics, weak immunity, facility to be colonized, and who often receive invasive procedures [4–7].

Many studies are available comparing the clinical characteristics of BSIs due to the same bacterium type with the resistance to different drugs, but few studies compare BSIs caused by different GNB. Each bacterium has its own pathogenic characteristics, mainly resulting in different vulnerable population and mortality. Recent studies found that the multi-drug resistance (MDR)-A. baumannii BSI has an alarming death rate, exceeding 70% in the ICU [8–10]. However, the reported mortality of BSIs in the ICU caused by K. pneumoniae [8], E. coli [11, 12] and P. aeruginosa [13] was approximately 40%. According to the current

situation, the aim of this study was to analyze the clinical characteristics of MDR-A. baumannii BSI and other GNB BSIs, and the prognostic factors of MDR-A. baumannii BSI.

Methods

Study design and patient selection

This was a retrospective observational study conducted at the Affiliated Lianyungang Hospital of Xuzhou Medical University with 2500 beds in China. ICU patients with BSIs due to MDR-*A. baumannii*, MDR-*K. pneumoniae*, MDR-*P. aeruginosa* and MDR-*E. coli* from Feb 2013 to Sep 2019 were included and analysed in this study, respectively including 96, 147, 65, 76 bacteremic episodes. The inclusion criteria were the following: (1) age ≥ 18 years; (2) blood culture positive for MDR-*A. baumannii*, MDR-*K. pneumoniae*, MDR-*P. aeruginosa*, MDR-*E. coli*; (3) clinical symptoms consistent with infection. Multiple positive cultures associated to the same patient were considered as one episode. Our study was conducted according to the principles stated in the Declaration of Helsinki and has been approved by local Ethical Committees (YJ-20190625001).

Clinical data collection

Pre-designed questionnaires were used to collect patient data from the Electronics Medical Records management system or clinical charts. The following information was reviewed: demographics; microbial drug resistance; comorbidities; cause of ICU admission; source of infection; microorganism colonization or infection prior to BSIs; Length of ICU stay within 30 days before infection; length of hospitalization before infection; albumin level before infection; previous chemotherapy or radiotherapy; antibiotics received before infection; transfusion before infection; previous steroid treatment; neutropenia before infection; parenteral nutrition before infection; acute physiological and chronic health assessment (APACHE II) score; all-cause 28-day mortality. As regard MDR-*A. baumannii* BSI, the immune response after infection by leukocyte and neutrophil changes was also evaluated, and the function of the organ or system after infection. Infections were not treated with colistin because it was not available in our hospital.

Definitions

The infection caused by MDR-*A. baumannii* or other GNB was defined as clinical signs of the systemic inflammatory response syndrome and positive culture. Infection onset was defined as the date of collection of the first positive blood culture for the observed pathogen. Primary bacteraemia was recorded if no source was identified. Before the infection onset, isolation of any microorganisms in other sites such as urine, lung, abdomen and skin were recorded as microorganism colonization or infection. Neutropenia was defined as an absolute neutrophil count < 1500/μl. Weak leukocyte response was defined as leucocyte lower than the pre-infection level by multiple tests within 2 days after the infection onset. Neutrophil deficiency was defined as an absolute neutrophil count < 500/μl. Prior antibiotic therapy was defined as the use of antibiotics for > 48 h within the 30 days before the infection onset. Steroid treatment was defined as an administration > 20 mg/day of prednisone (or its equivalent) for 3 or more days.

Sensitive antibiotic therapy was defined as the therapy with at least one agent which has *in vitro* activity against the infecting pathogen. Length of ICU and hospitalization stay were expressed by the number of days from the date of admission to the date of the infection onset. Septic shock was defined according to the international consensus definition [14]. MDR was defined as the resistance to at least one agent in three or more categories of antibiotics [15].

Bacterial isolation and identification

Isolated bacteria were identified by the Vitek 2 system (bioMérieux, Marcy l'Etoile, France). According to the Clinical and Laboratory Standards Institute, the drug susceptibility test was performed by disk diffusion method or dilution method. Extended spectrum beta-lactamases (ESBLs) production was tested by disk diffusion method. Colistin resistance test was not routinely carried out in our hospital, but the strains included in our study were all sensitive to colistin when the susceptibility test was performed.

Statistical analysis

Statistical analysis was performed using SPSS version 23.0. Continuous variables were presented as mean ± standard deviation (by Student's *t*-test) or as the median (the upper quartile, the lower quartile) (by Kruskal Wallis rank-sum test) when the distribution was not normal. Categorical variables were described by frequency (percentage), using the Chi-square test or Fisher exact test. Cox risk proportion model was used, variables with statistical significance in the univariate analysis were included in the multivariate model, and stepwise forward regression was used to screen variables; the entry criterion was 0.05, and the exclusion criterion was 0.10. Time to mortality was analysed using the Kaplan-Meier survival curve and the log-rank test by Graphpad Prism 6.0. $P<0.05$ was considered statistically significant, and all the tests were 2-tailed.

Results

BSI characteristics by different GNB

Patient characteristics are summarized in Table 1. Twenty-seven (35.5%) cases of MDR-*E. coli* BSI were considered as community-acquired BSIs (which occurred before or within 48 hours after admission), all the rest were hospital-acquired BSIs.

The average age of patients with MDR-*P. aeruginosa* and MDR-*E. coli* BSIs was approximately 5 years younger than that of the other two groups ($P=0.002$). In patients with MDR-*A. baumannii* and MDR-*K. pneumoniae* BSIs, the prevalence rate of underlying diseases was high, especially chronic lung disease ($P=0.003$) and chronic kidney disease ($P<0.001$). In addition to MDR-*E. coli* BSI group, approximately half or more than half patients in other groups were admitted to ICU due to severe pneumonia and respiratory failure (both $P<0.001$). The proportion of patients with MDR-*E. coli* BSI admitted to ICU due to urinary tract infection, abdominal infection, shock, renal failure, and post-operation complications were higher than the

proportion of other BSIs (shock *P*=0.009, other *P*<0.001). Admission to ICU due to burns was more commonly characterized by MDR-*P. aeruginosa* BSI (*P*<0.001) compared to other BSIs.

Central venous catheter (CVC) (*P*=0.037) and pneumonia (*P*<0.001) as the source of infection were more commonly characterized by MDR-*A. baumannii* and MDR-*K. pneumoniae* BSIs, while intra-abdominal and urinary tract infections (all *P*<0.001) were more commonly characterized by MDR-*E. coli* BSIs compared with other BSIs. Patients with MDR-*P. aeruginosa* BSIs showed a higher frequency of skin and soft tissue infections (*P*=0.001) than those with other BSIs. The MDR-*E. coli* BSI was the one less characterized by a previous infection or colonization by any microorganisms, while the MDR-*A. baumannii* BSI was the one mostly characterized by a previous fungal infection or colonization (*P*=0.008). CVC, invasive mechanical ventilation, tracheotomy, nasogastric tube or nasointestinal tube, and urinary tube were often characterized by MDR-*A. baumannii* BSI, but rarely characterized by MDR-*E. coli* BSI compared with other BSIs (tracheotomy, *P*=0.003, other, *P*<0.001). Before the infection onset, the length of ICU stay and hospitalization (all *P*<0.001) were the longest in the MDR-*A. baumannii* BSI group, and the shortest in the MDR-*E. coli* BSI group. A significant difference in albumin content was observed before the infection onset (*P*<0.001). Treatment with 3 or more classes of antibiotics was more common in the MDR-*A. baumannii* group and MDR-*K. pneumoniae* BSI group (*P*<0.001). Mortality was significantly different among the groups (*P*<0.001), with MDR-*A. baumannii* having the highest mortality.

Analysis of the antibiotic resistance rate

Antibiotic resistance is shown in table 2. In the MDR-*K. pneumoniae* group, 41 (27.9%) were infected with ESBLs-producing strains, while in the MDR-E. coli group, 56 (73.7%) were infected with ESBLs-producing strains. The resistance rates of MDR-*A. baumannii*, MDR-*K. pneumoniae*, MDR-*P. aeruginosa* and MDR-*E. coli* to imipenem were 95.8%, 75.5%, 44.6% and 9.2%, respectively. MDR-*A. baumannii* had relatively low resistance to amikacin and sulfamethoxazole trimethoprim (53.1% and 64.6%, respectively). Ad regard MDR-*K. pneumoniae*, the resistance to tigecycline was the lowest (31.3%). The resistance rate of MDR-*P. aeruginosa* to piperacillin tazobactam, amikacin, ceftazidime and levofloxacin ranged from 23 to 31%. Overall, MDR-*E. coli* had the lowest drug resistance rate, but the resistance rate for levofloxacin was relatively high (71.9%).

Risk factors related to the mortality of MDR-*A. baumannii* BSI

COX regression analysis of risk factors related to the outcome of MDR-*A. baumannii* BSI is shown in table 3. APACHE II score (HR 1.13, CI 95% 1.04-1.23, *P*=0.005), previous steroid treatment (HR 2.18, CI 95% 1.24-3.84, *P*=0.007) and deterioration of the circulatory system (septic shock) after infection (HR 2.14, CI 95% 1.18-3.89, *P*=0.013) were associated with increased 28-day mortality, while high albumin level (HR 0.918, CI 95% 0.86-0.98, *P*=0.01) was related to higher 28-day survival.

Finally, the Kaplan-Meier analysis of the 28-day survival of patients in each BSI group is reported in Fig. 1. As regard MDR-*A. baumannii* BSIs, the Kaplan-Meier analysis of 28-day survival of patients associated with a previous steroid treatment and septic shock was also reported.

Discussion

This study demonstrated that BSI caused by different GNB had significantly different clinical characteristics by comparing the risk factors such as causes of ICU admission, underlying diseases, sources of infection, treatment and invasive procedures.

MDR-*K. pneumoniae* BSIs

A meta study [16] found that the main risk factors for carbapenem-resistant *K. pneumoniae* (CR *K. pneumoniae*) infection included: long hospital stay or ICU stay, previous use of carbapenems and steroids, CVC implantation, mechanical ventilation and tracheostomy, with the first three as the major risk factors. Our study found that all the above risk factors included a higher proportion of *K. pneumoniae* infections (mainly CR *K. pneumoniae*), but a less proportion of *A. baumannii* infection, compared with *P. aeruginosa* and *E. coli* infection. Other studies [8, 17, 18] have confirmed some of the above risk factors, and found that CR *K. pneumoniae* colonization is a strong risk factor for later infection. In our study, *K. pneumoniae* was found in 64.6% of patient specimens before the infection onset, and most of them were colonized bacteria. *K. pneumoniae* can asymptomatically colonize the skin, mouth, respiratory tract and intestines, and intestinal colonization is closely related to subsequent infections [19-21]. Thus, we suspected that *K. pneumoniae* in this study might mainly come from the direct or indirect gut microbiota. One study found that the intestinal decontamination can decrease the incidence rate of ICU-acquired GNB BSI by 45%, while the selective oropharyngeal decontamination only decreased by 33% [22]. However, in a randomized trial of 8665 patients [23], oropharyngeal decontamination or SDD did not reduce mortality in ICU-acquired MDR-GNB BSI compared with the standard care. The all-cause mortality in our study was 63.3%, thus higher than 44.5% [8] (mortality due to CR *K. pneumoniae* BSI in ICU patients). Another study [24] found that mortality rates varied with severity, since in high-risk patients the mortality rate of CR *K.* pneumoniae BSI is 77%, while it is 45% in middle-risk patients. Therefore, we hypothesized that the mortality was closely related to the general condition and treatment strategy.

MDR-*E. coli* BSIs

Although *E. coli* is present in the normal intestinal flora, it can enter and survive in a sterile parenteral environment, which often leads to urinary tract infections and BSI [25]. Indeed, *E. coli* is the most important pathogenic bacteria in urinary and abdominal infections [26] and BSI. One study reported that 76% of *E. coli* BSIs come from home, and the most common source of home-acquired *E. coli* BSIs was the urinary tract, while the gastrointestinal tract was the common source for nosocomial *E. coli* BSIs [27]. Our observations were similar with the above observations. Patients in the *E. coli* group were admitted to the ICU mainly for septic shock or renal failure secondary to urinary or abdominal infection, and BSI often occurred within 48 hours after the transfer from the general ward or community to the ICU, thus, the previous duration of hospital stay and ICU stay were short. In this study, most MDR-*E. coli* were ESBLs-producing strains and Ajao et al. [28] found that colonization and exposure to multiple antibiotics are independent risk factors for infection with *E. coli*-producing ESBLs. However, these factors were not significantly present in our study due to short hospital stay and unclear out-of-hospital medication for

some patients. Overall, the *E. coli* group was significantly different from the other groups due to its special source of infection, and the mortality rate was low thanks to the ease of keeping its infections under control and easy access to sensitive antibiotics.

MDR-*P. aeruginosa* BSIs

Unlike other bacteria, *P. aeruginosa* not only has high virulence, but also has inherent resistance to some antibiotics and is prone to drug resistance. Our study found that *P. aeruginosa* BSIs were common in immunocompromised patients with a previous chemoradiotherapy and neutropenia, Mccarthy et al. found similar findings [29]. In our study, patients after surgery often developed *P. aeruginosa* BSI, which might be related to the previous intestinal colonization [30, 31]. Indeed, *P. aeruginosa* often causes pneumonia and can escape from the lungs by destroying the pulmonary vascular barrier to cause BSI [32]. This might explain the pulmonary origin of *P. aeruginosa* BSI in our study. Similar to other studies [3, 33], but different from the other groups, in the present study *P. aeruginosa* often caused burn wound infection, which subsequently led to BSI. The 30-day mortality rate was 41.5% in our study, similar to the 37% reported by other studies [30]. Thaden et al. found that *P. aeruginosa* BSI is related to increased mortality compared with other GNB BSIs, and this effect persists after adjustment for comorbidities, resistance, and treatment factors [34], thus, *P. aeruginosa* virulence might play an important role in lethality. However, by vertical comparison of the risk factors leading to death on day 2, 7, and 28 after *P. aeruginosa* BSI, Mccarthy [29] et al. found that from day-7 onwards patient comorbidities become increasingly important, suggesting that the 30-day mortality depends on the underlying disease to some extent.

MDR-*A. baumannii* BSIs

It is well known that ICU is a very common place to contract an infection, especially from *A. baumannii*, which mainly includes the following two reasons. As regard patient's factors: long hospital stay [5], experience of invasive procedures (CVC [35], surgery [1, 36], mechanical ventilation [37]), exposure to antibiotics [1, 36] such as carbapenems, weak immunity (previous hormone therapy [36], tumor patients with neutropenia [38]). As regard the contamination of wards [39] *A. baumannii* is a bacterium commonly present in ICU that is difficult to eliminate and it often spreads among the ward crowd, resulting in a high risk of *A. baumannii* colonization for patients [40, 41]. Some of these aspects were also found in our study. Compared with other groups, *A. baumannii* group had the longest hospitalization or ICU stay, the highest total proportion of invasive operations, and exposure to more than 3 classes of antibiotics (carbapenem and piperacillin tazobactam were the main antibiotics used). Our hypothesis is that it is difficult to reduce the occurrence of *A. baumannii* infection in ICU, except for the decontamination and improvement of the awareness of the cleaning operations of the medical workers.

Drug resistance

Carbapenems were often selected for empirical treatment in our study, which is an important factor causing the onset of carbapenem-resistant *A. baumannii*, *K. pneumoniae* and *P. aeruginosa*. Carbapenems and tigacycline were rarely used in *E. coli* group when admitted to hospital, thus, the resistance rate was

significantly lower in this group. However, with drug-resistant genes resulting in drug-resistant bacteria, they can widely spread in hospitals and communities, consequently resulting in an increased incidence of carbapenem-resistant *E. coli* and CR *K. pneumoniae* infections in China [42]. In China, ST11 has been considered as the dominant CR *K. pneumoniae* strain, but new ST11 CR *A. baumannii* is emerging [43], which is hypervirulent, multidrug resistant, and transmissible, potentially resulting a real superbacteria that could pose a serious threat to public health. The polycolisin-resistant *E. coli* has been found in China [42], which undoubtedly adds to the current sad situation.

Prognostic analysis of MDR-*A. baumannii* BSIs

Overall, previous studies found that the prognosis of *A. baumannii* BSI in ICU patients is different depending on the underlying disease, illness severity, drug resistance, therapies used, post-infection appearance and infection source. The following characteristics often lead to poor prognosis: improper initial antibiotic treatment [9, 38], comorbidities (tumours [38, 44, 45], liver cirrhosis [46], chronic obstructive pulmonary disease and chronic renal failure [37]), high drug resistance, neutropenia [38], previous high-dose hormone therapy [47], previous surgery[9], infection originated from the respiratory tract [35, 46], high SAPS score [8], Pitt score[35], APACHE II score [37, 38, 46]. However, the development of septic shock [47] and the severity of the disease are the factors most closely related to prognosis, and our study also found these two key points. A study [9] focused on ICU patients found that patients developing septic shock after MDR-*A. baumannii* BSI have a 23.8% higher mortality rate than patients without septic shock (82.5% *vs* 58.7%). An early study [10] grouped by APACHE II score found that the mortality of 15 < APACHE II scores ≤ 25 group was 14.3%, and the mortality of 25 < APACHE II scores ≤ 35 group was 3 times of that of 15 < APACHE II scores ≤ 25 group. In addition, Yang et al. found that in case of *A. baumannii* BSI, the death rate of the carbapenem MICs ≥ 8 mg/l group was twice that of the MICs ≤ 48 mg/l group [48]. In our study, hypoalbuminemia and a previous hormone therapy were independently associated with death, suggesting that nutritional and immune statuses are very important. Because the access to colistin was limited in our hospital, common drug treatments mainly included tigecycline in combination with cefoperazone/sulbactam, and monotherapy with amikacin or sulfamethoxazole trimethoprim, but none of the monotherapies has been reported as associated with survival. In addition, *in vitro* treatments with sensitive antibiotics that improved the prognosis were not found.

Limitations and strengths

Some limitations are present in this study. Firstly, this was an observational research with its inherent defects. Secondly, it is a single-centre study with relatively few cases included, thus, differences between groups could not reflect a common situation worldwide. Thirdly, in the analysis of the prognosis, the adjustment for the severity of the disease and antibiotic regimen was not performed. However, this study was based on ICU patients, reducing the influence of ward difference and convenient to compare among patients of similar illness severity. The clinical characteristics of four common MDR-GNB BSIs in ICU were compared to better identify the characteristics of different BSIs. In addition, the response of vital organs or systems after infection was evaluated in order to explore the pathogenicity of MDR-*A. baumannii* BSI.

Conclusion

In general, the clinical features of BSIs were significantly different among each other, especially in infection sources and reasons of ICU admission of P. aeruginosa and E. coli group. MDR-A. baumannii BSIs often occurred in patients who had long hospital stay or ICU stay and accepted various invasive operations. MDR-A. baumannii BSI had a very poor prognosis and the development of septic shock, hormone therapy, APACHE II score, high albumin level were independent risk factors affecting the prognosis. Due to the difficulty in the treatment, clinicians should pay special attention to prevent the occurrence of infection.

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Tables

TABLE 1 Comparison of clinical features of the four kinds of BSIs

Variables	MDR-*A. baumanni* (n=96)	MDR-*K. pneumoniae* (n=147)	MDR-*P. aeruginosa* (n=65)	MDR-*E. coli* (n=76)	P
Age, mean ± SD (years)	66.7 ± 16.1	66.5 ± 13.8	62.1 ± 14.9	60.7 ± 11.3	0.002
APACHE scores	26.1 ± 3.7	27.0 ± 3.9	25.9 ± 4.2	25.6 ± 5.1	0.072
Male sex	63 (65.6%)	100 (68.03%)	42 (64.6%)	44 (57.9%)	0.514
Underlying diseases					
Diabetes	26 (27.1%)	40 (27.2%)	15 (23.1%)	22 (28.9%)	0.884
Angiocardiopathy	57 (59.4%)	78 (53.1%)	28 (43.1%)	32 (42.1%)	0.073
Cerebrovascular disease	32 (33.4%)	48 (32.7%)	20 (30.8%)	13 (17.1%)	0.070
Chronic lung disease	23 (24.0%)	27 (18.4%)	5 (7.7%)	5 (6.6%)	0.003
Chronic kidney diseases	24 (25.0%)	15 (10.2%)	4 (6.2%)	4 (5.3%)	<0.001
Chronic liver disease	7 (7.3%)	5 (3.4%)	0 (0.0%)	4 (5.3%)	0.132
Rheumatic disease	10 (10.4%)	11 (7.5%)	4 (6.2%)	5 (6.6%)	0.721
Neoplasm	11 (11.5%)	21 (14.3%)	15 (23.1%)	13 (17.1%)	0.228
Leukemia	5 (5.2%)	5 (3.4%)	4 (6.2%)	3 (4.0%)	0.800
Other	13 (13.5%)	6 (4.1%)	4 (6.2%)	3 (4.0%)	0.022
Cause of ICU admission					
Severe pneumonia	62 (64.6%)	82 (55.8%)	32 (49.2%)	18 (23.7%)	<0.001
Urinary system infection	6 (6.3%)	8 (5.4%)	3 (4.6%)	16 (21.1%)	<0.001
Abdominal infection	8 (8.3%)	24 (16.3%)	10 (15.4%)	28 (36.8%)	<0.001
Other infections	6 (6.3%)	6 (4.1%)	3 (4.6%)	1 (1.3%)	0.453
Shock	50 (52.1%)	65 (44.2%)	27 (41.5%)	50 (65.8%)	0.009
Respiratory failure	61 (63.5%)	98 (66.7%)	49 (75.4%)	29 (38.2%)	<0.001
Renal failure	17 (17.7%)	14 (9.5%)	13 (20.0%)	24 (31.6%)	<0.001
Liver failure	6 (6.3%)	5 (3.4%)	3 (4.6%)	2 (2.6%)	0.628
Trauma	12 (12.5%)	18 (12.2%)	5 (7.7%)	10 (13.2%)	0.737
Extensive burns	3 (3.1%)	0 (0.0%)	6 (9.2%)	0 (0.0%)	<0.001
Stroke	6 (6.2%)	15 (10.2%)	3 (4.6%)	2 (2.6%)	0.149
Postoperation	10 (10.4%)	13 (8.8%)	16 (24.6%)	22 (28.9%)	<0.001
After cardiopulmonary resuscitation	8 (8.3%)	15 (10.2%)	2 (3.1%)	4 (5.3%)	0.262
Source of infection					
CVC-related bacteremia	17 (17.7%)	20 (13.6%)	6 (9.2%)	3 (4.0%)	0.037
Pneumonia	34 (35.4%)	58 (39.5%)	12 (18.5%)	2 (2.6%)	<0.001
Intra-abdominal	11 (11.5%)	24 (16.3%)	12 (18.5%)	40 (52.6%)	<0.001
Urinary tract	3 (3.1%)	10 (6.8%)	4 (6.2%)	22 (29.0%)	<0.001

Skin or soft tissue	3 (3.1%)	7 (4.8%)	10 (15.4%)	1 (1.3%)	0.001
Primary bacteremia	28 (29.2%)	28 (19.1%)	21 (32.3%)	8 (10.5%)	0.004
Previous microorganism colonization/infection					
The same kind	45 (46.9%)	95 (64.6%)	33 (50.8%)	27 (35.5%)	<0.001
Other bacteria	47 (49.0%)	62 (42.2%)	29 (44.6%)	8 (10.5%)	<0.001
Fungus	18 (18.8%)	12 (8.1%)	4 (6.2%)	4 (5.3%)	0.008
Invasive procedures					
Previous surgery	27 (28.1%)	55 (37.4%)	30 (46.2%)	28 (36.8%)	0.134
CVC	78 (81.3%)	98 (66.7%)	45 (69.2%)	30 (39.5%)	<0.001
Abdominal drainage	17 (17.7%)	25 (17.0%)	15 (23.1%)	19 (25.0%)	0.437
Thoracic drainage	15 (15.6%)	14 (9.5%)	8 (12.3%)	5 (6.6%)	0.254
Invasive mechanical ventilator	77 (80.2%)	96 (65.3%)	39 (60.0%)	18 (23.7%)	<0.001
Tracheostomy	34 (35.4%)	48 (32.7%)	10 (15.4%)	13 (17.1%)	0.003
CRRT	23 (24.0%)	23 (15.7%)	5 (7.7%)	8 (10.5%)	0.021
Nasogastric tube or nasointestinal tube	90 (93.8%)	123 (83.7%)	46 (70.8%)	28 (36.8%)	<0.001
Urinary catheter	91 (94.8%)	117 (79.6%)	52 (80.0%)	31 (40.8%)	<0.001
Other	11 (11.5%)	18 (12.2%)	5 (7.7%)	8 (10.5%)	0.801
Length of ICU stay, mean ± SD (days)	28.8 ± 29.8	13.8 ± 7.4	9.6 ± 9.3	5.4 ± 9.6	<0.001
median (Q1-Q3)	18.0 (9.0-35.0)	14.0 (9.0-17.0)	7.0 (4.0-12.0)	1.0 (1.0-3.2)	<0.001
Length of hospitalization, mean ± SD (days)	42.6 ± 36.0	23.2 ± 10.0	18.8 ± 13.1	8.8 ± 10.5	<0.001
median (Q1-Q3)	29.0 (19.0-53.5)	21.0 (18.0-29.0)	17.0 (9.0-25.0)	4.5 (1.8-13.0)	<0.001
Albumin, mean ± SD (g/l)	27.0 ± 4.5	27.8 ± 4.1	28.7 ± 3.5	26.1 ± 4.8	<0.001
Prior chemotherapy or radiotherapy	7 (7.3%)	9 (6.1%)	10 (15.4%)	3 (4.0%)	0.056
Prior steroid treatment	31 (32.3%)	46 (31.3%)	20 (30.8%)	8 (10.5%)	0.004
Prior antibiotic therapy (1-2 categories)	42 (43.8%)	62 (42.2%)	38 (58.5%)	33 (43.4%)	0.151
Prior antibiotic therapy (≥3 categories)	51 (54.8%)	82 (55.8%)	26 (40.0%)	9 (11.8%)	<0.001
Neutropenia (prior to BSI)	6 (6.3%)	15 (10.2%)	10 (15.4%)	4 (5.3%)	0.132
Parenteral nutrition	24 (25.0%)	27 (18.4%)	16 (24.6%)	5 (6.6%)	0.010
28-day mortality	69 (71.9%)	93 (63.3%)	27 (41.5%)	29 (38.2%)	<0.001

BSI: bloodstream infection; ICU: intensive care unit; SD: standard deviation; Q1: 1st quartile; Q3: 3rd quartile; APACHE: cute physiology and chronic health evaluation; CVC: central venous catheter; CRRT: continuous renal replacement therapy.

TABLE 2 Comparison of drug resistance

Antimicrobial agent	MDR-*A. baumannii* (n=96)	MDR-*K. pneumoniae* (n=147)	MDR-*P. aeruginosa* (n=65)	MDR-*E. coli* (n=72)
	R (%)	R (%)	R (%)	R (%)
Imipenem	95.8	75.5	44.6	9.2
Piperacillin tazobactam	97.9	85.0	23.1	17.1
Ceftazidime	94.8	68.0	30.8	31.6
Levofloxacin	89.6	89.1	30.8	77.6
Amikacin	53.1	65.3	27.7	9.0
Sulfamethoxazole trimethoprim	64.6	80.2	80.0	67.1
Tigecycline	83.3	31.3	86.2	0.0

TABLE 3 Univariate and multivariate Cox regression analysis about factors associated with 28-day mortality in MDR-*A. baumannii* BSIs

Variables	Survivor	Non-Survivor	univariate analysis				multivariate analysis			
	(n=27)	(n=69)	HR	95% CI		P	HR	95% CI		P
				lower	upper			lower	upper	
Age, mean ± SD (years)	62.1 ± 20.9	68.4 ± 13.5	1.008	0.994	1.022	0.288				
Female sex	10 (37.0%)	23 (33.3%)	0.950	0.576	1.567	0.840				
APACHE scores	27.1 ± 3.2	24.1 ± 3.7	1.141	1.064	1.223	0.000	1.131	1.039	1.231	0.005
Underlying diseases										
Diabetes	6 (22.2%)	20 (29.0%)	1.060	0.630	1.783	0.827				
Angiocardiopathy	17 (63.0%)	40 (58.0%)	0.818	0.507	1.320	0.411				
Cerebrovascular disease	13 (48.1%)	19 (27.5%)	0.545	0.320	0.931	0.026				
Chronic lung disease	5 (18.5%)	18 (26.1%)	1.265	0.738	2.167	0.393				
Chronic kidney diseases	4 (14.8%)	20 (29.0%)	1.095	0.650	1.846	0.733				
Chronic liver disease	1 (3.7%)	6 (8.7%)	1.324	0.573	3.062	0.512				
Rheumatic disease	2 (7.4%)	8 (11.6%)	1.351	0.646	2.826	0.424				
Neoplasm	3 (11.1%)	8 (11.6%)	0.942	0.450	1.970	0.874				
Leukemia	4 (14.8%)	1 (1.4%)	0.176	0.024	1.272	0.085				
Invasive procedures										
Previous surgery	8 (29.6%)	19 (27.5%)	0.954	0.563	1.619	0.863				
CVC	19 (70.4%)	59 (85.5%)	1.492	0.763	2.920	0.242				
Abdominal drainage	3 (11.1%)	14 (20.3%)	1.173	0.652	2.110	0.594				
Thoracic drainage	3 (11.1%)	12 (17.4%)	1.178	0.632	2.196	0.606				
Invasive mechanical ventilator	20 (74.1%)	57 (82.6%)	1.425	0.764	2.657	0.265				
Tracheostomy	13 (48.1%)	21 (30.4%)	0.693	0.414	1.160	0.693				
CRRT	6 (22.2%)	17 (24.6%)	1.121	0.648	1.940	0.682				
Prior antibiotic therapy (≥3categories)	16 (61.5%)	35 (52.2%)	0.871	0.539	1.408	0.574				
Neutropenia (prior to BSI)	1 (3.7%)	5 (7.2%)	1.251	0.502	3.114	0.631				
Prior steroid treatment	5 (18.5%)	27 (39.1%)	1.982	1.213	3.238	0.006	2.183	1.242	3.840	0.007
Albumin , mean ± SD (g/l)	30.0 ± 4.9	25.7 ± 3.6	0.910	0.861	0.962	0.001	0.918	0.861	0.979	0.010
Sensitive antibiotic therapy	9 (33.3%)	23 (33.3%)	0.852	0.516	1.407	0.532				
Length of ICU stay (prior to BSI), median (Q1-Q3)	18.0 (8.0-	17.0 (9.5-	0.996	0.987	1.004	0.328				

	49.0)	29.0)								
Length of hospitalization (prior to BSI), median (Q1-Q3)	32.0 (17.0-85.0)	28.0 (19.0-50.0)	0.995	0.988	1.002	0.170				
Immunoreaction										
Weak leukocyte response	5 (18.5%)	10 (14.5%)	0.864	0.442	1.690	0.670				
Neutropenia	1 (3.7%)	7 (10.1%)	1.283	0.587	2.805	0.532				
Neutrophil deficiency	0 (0.0%)	2 (2.9%)	5.125	1.218	21.573	0.026				
Deterioration of system										
Respiratory	9 (33.3%)	37 (53.6%)	1.402	0.873	2.254	0.162				
Circulatory (septic shock)	6 (22.2%)	50 (72.5%)	3.245	1.897	5.550	0.000	2.138	1.175	3.890	0.013
Hepatic	7 (25.9%)	24 (35.3%)	1.410	0.857	2.321	0.176				
Coagulative	6 (22.2%)	25 (36.8%)	1.529	0.932	2.506	0.093				
Renal	3 (11.1%)	27 (39.1%)	2.464	1.507	4.030	0.000				

CI: confidence interval; HR: hazard ratio; SD: standard deviation; BSI: bloodstream infection; Q1: 1st quartile; Q3: 3rd quartile; APACHE: cute physiology and chronic health evaluation; CVC: central venous catheter; CRRT: continuous renal replacement therapy; ICU: intensive care unit.

Declarations

Conflict of interest: The authors declare that they have no conflict of interest.

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Ethical Standards and Approval: The study was conducted in accordance with the ethical standards of the Helsinki declaration and its later amendments and approved through Research Ethics Committee of the Affiliated Lianyungang Hospital of Xuzhou Medical University in China.

Figures

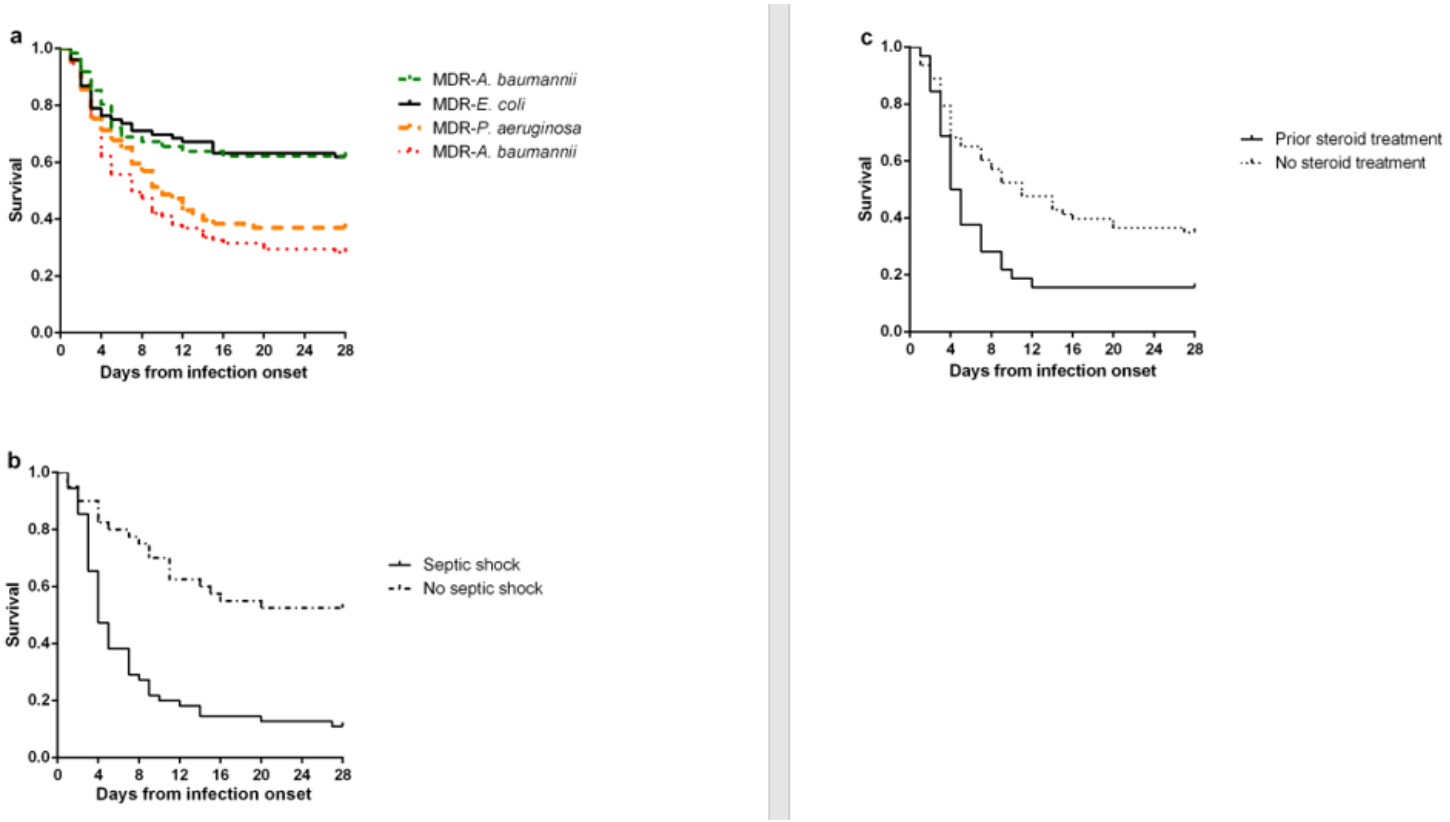

Figure 1

a. Kaplan-Meier curves for 28-day survival of BSIs due to MDR-A. baumannii, MDR-K. pneumoniae, MDR-P. aeruginosa and MDR-E. coli (P<0.001). b. Kaplan-Meier curves for 28-day survival of MDR-A. baumannii BSIs causing septic shock (P<0.001). c. Kaplan-Meier curves for 28-day survival of MDR-A. baumannii BSIs with previous steroid treatment (P=0.009).