Epidemiology and microbiology of Gram-negative bloodstream infections in a tertiary-care hospital in Beijing, China: a 9 -year retrospective study

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Research

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Abstract

Background

Gram-negative bacterial bloodstream infections (BSIs) are serious diseases associated with high morbidity and mortality. The following study examines the incidence, clinical characteristics and microbiological features, drug resistance situations and mortality associated with gram-negative BSIs at a large Chinese tertiary-care hospital in Beijing, China.

Methods

A retrospective cohort study of patients with gram-negative BSIs was performed between January 1, 2010, and December 31, 2018, at the Chinese People's Liberation Army General Hospital. The patients' data were collected and included in the reviewing electronic medical records.

Results

A total of 6867 episodes of gram-negative BSIs occurred among 3199 patients over 9 years, and there were 3032 significant BSI episodes 77% of these cases were healthcare-associated, while 23% were community-associated. The overall incidence of gram-negative BSIs fluctuated from 2.30 to 2.55 episodes per 1000 admissions over 9 years. Malignancy was the most common comorbidity and indwelling central intravenous catheter was the most common predisposing factor for gram-negative BSI. *Escherichia coli* were the major pathogen (34.3%), followed by *Klebsiella pneumoniae* (23.3%) and other bacterial pathogens (9.9%). The resistance rates of *Escherichia coli* and *Klebsiella pneumoniae* to penicillins were more than 90%. and the resistance rates of *Acinetobacter baumannii* to the most antibiotic were more than 70% include the Carbapenem. The resistance of ESBLs-producing *Escherichia coli* to the most antibiotic was higher than non-ESBLs producing *Escherichia coli* but to Carbapenems(0.7% VS 5.1%). The rates of Carbapenems resistance of ESBLs-producing *Klebsiella pneumoniae* and non-ESBLs producing *Klebsiella pneumoniae* were 32.8% and 8.1%. The rates of Carbapenems resistance of Enterobacter cloacae and Pseudomonas aeruginosa were 1.4% and 27.8% respectively. Between 2010 and 2018, the overall mortality of gram-negative BSIs decreased from 11.41–9.05%(X^2 = 6.95, P = 0.434). Moreover, the mortality in the ICU decreased from 27.03–14.93%(X^2 = 9.61, P = 0.212), while in the general ward fluctuated from 8.85–8.13% that without obvious decrease change(X^2 = 9.29, P = 0.232).

Conclusions

The mortality of gram-negative BSIs have showed downward trends. carbapenem antibiotics is still consider the best treatment for patients with Gram-negative BSIs except *Acinetobacter baumannii*.

Introduction

BSIs are serious diseases associated with high morbidity and mortality, which are difficult to treat and often result in a heavy social and economic burden, and gram-negative bacteria have been reported as the prevalent cause of BSIs in many studies[1, 2, 3, 4]. The *Escherichia coli*, *Klebsiella spp.*, *Acinetobacter spp. Pseudomonas aeruginosa* were the top 4 gram-negative bacterial species found in all clinical samples obtained from Chinese hospital according to a CHINET surveillance in 2016[5, 6], and the multi-drug resistance (MDR) gram-negative bacteria has poor clinical treatment effect and high mortality rate, especially the gram-negative bacteria with extended spectrum beta-lactamases(ESBLs) and carbapenem-resistant Enterobacteriaceae(CRE) which have resulted in difficult-to-treat or even untreatable cases and caused the increase in mortality. Mortality from CRE infection was reported by the China CRE Network to be as high as 33.5%, and most cases were determined to be caused by carbapenem-resistant *E. coli* (CREC) and *K. pneumoniae* (CRKP)[7]. In addition, a report from Europe has shown that there were more than 1.2 million episodes of BSIs with 157000 deaths per year, while between 57500 and 677000 episodes of BSIs were reported in North America causing some 79000 to 94000 deaths [11]. Other studies also have reported that the morbidity and mortality of BSIs varies from country to country [8, 9, 10] .

Over recent years, due to the widespread use of antibiotics, immunosuppressants and anti-tumour drugs, and the increase of invasive medical examinations and treatments, the epidemiology and antimicrobial resistance have been changing, although many studies have reported the rate of carbapenem-resistant bacterial has steadily increased in recent years which has result in higher patient morbidity, mortality and economic burden for different gram-negative bacterial, but lack of studies with large sample size to report the epidemiology and drug resistance of gram-negative bacteria bloodstream infections in general and in different periods and regions, thus making it very difficult to timely choose antibiotic treatment based on the empirical evidence. Therefore, the purpose of this study was to provide more data on the incidence, microbiological features, mortality and drug resistance data of gram-negative bacterial in china.

Materials And Methods

We performed a retrospective cohort study in patients with gram-negative bacterial bloodstream infections between January 1, 2010, and December 31, 2018 at the Chinese People's Liberation Army General Hospital (PLAGH) in Beijing, China.

Eligible patients included all hospitalized patients with at least one positive blood culture for gram-negative bacteria. In patients with persistent BSIs caused by the same organism, only the first episode was included within the previous 30 days. If patients had 2 or more separate BSIs, each infection was considered individually. All patients were identified by searching the real-time nosocomial infection surveillance system (RT-NISS)[12]. This platform utilizes data from electronic medical record systems, such as sex, hospital ward, comorbidity, and microbiology results, with the application of clinically validated algorithms to identify and classify all of the patients' infections.

Data Collection

The patients' data were collected through review electronic medical records. We recorded the demographic data, including age and sex, the clinical data included predisposing factors, the hospitalization wards and comorbidities. The microbiological data included species of gram-negative bacteria, likely sources of BSIs (identified by treating doctors and/or physicians of the infection management and disease control department), and antimicrobial susceptibility results. We also collected annual admission data to calculate incidence rates, which are expressed as the number of BSI episodes per 1,000 hospital admissions.

Definitions

The diagnosis of gram-negative bacterial BSIs had to meet the following criteria: 1) isolation of gram-negative bacteria from one or more blood cultures; 2) having one of the following symptoms: fever (> 38°C), chills, or hypotension; and 3) elimination of the possibility of contamination during the collection and cultivation of blood samples [13]. Healthcare-associated BSIs were defined as the first positive blood culture obtained ≥ 48 h after hospital admission and < 7 days after discharge in patients undergoing intensive outpatient therapy involving regular hospital contact or with no evidence of infection at admission[13]. An episode was defined as the positive isolation of the gram-negative bacteria from at least one blood culture sample from a patient and without a prior blood culture isolating the same bacteria within the previous 30 days [7]. Onset of BSIs was defined as the date when the blood culture was collected. Poly-microbial BSIs were defined as two or more different clinically important organisms isolated from one single blood culture sample or different blood culture samples within 48 h. Active agents were confirmed according to the antibiotic susceptibility testing.

Identification And Antibiotic Susceptibility Testing

Blood was cultured using a BacT/ALERT 3D system (Becton-Dickinson, Sparks, MD, USA) in the microbiology laboratory. Species identification was performed using the VITEK 2 system (BioMérieux, Marcy l'Etoile, France). Antibiotic susceptibility testing was performed using the VITEK 2 system or the Kirby-Bauer Disk Diffusion method (Oxoid, UK) according to the recommendations proposed by the Clinical and Laboratory Standards Institute (CLSI) [14].

Statistical analysis

Categorical variables are expressed as frequency counts and percentages with 95% confidence intervals (95% CIs). Continuous variables are expressed as medians and inter-quartile ranges. The incidence and mortality of gram-negative BSIs over these years were determined using chi-square test for trend. The comparison of categorical variables was performed using Pearson's chi-square test or Fisher's exact test, while the comparison of continuous variables was performed using the Mann-Whitney U test. The results with a 2-tailed p-value < 0.05 were considered statistically significant. All of the statistical analyses were performed using SPSS software, version 20.0 (IBM Corp, Armonk, NY, USA).

Results

Incidence and species distribution

In total, 6867 episodes of BSIs caused by gram-negative bacteria occurred among 3199 patients during the 9-year study period. Among 3199 patients with gram-negative BSIs, 404 were infectioned with two different species (> 30 days apart), and 1430 had 2 or more BSI with the same species < 30 days apart. Only the results for the first cases among repeat results were included, so there were 3032 significant BSI episodes and the demographics and clinical data were available collated for 2980 of these clinically relevent episodes.

Among all BSI isolates, the most common gram-negative bacterial species was *Escherichia* (34.3%), followed by *Klebsiella pneumoniae* (23.3%) and other bacterial pathogens (9.9%). The species proportions in each year are shown in **Table.1**. In addition, 77% of these cases were healthcare-associated infections, 23% were community acquired, and *Escherichia* was the most common isolate. For all gram-negative BSIs species, healthcare-associated infection was more common than community-acquired infection especially for *Acinetobacter baumannii*.

Table 1

The species ratio from 2010 to 2018

organisms	2010(610)	2011(713)	2012(874)	2013(683)	2014(762)	2015(922)	2016(1086)	2017(747)	2018(470)	total(6867)
Escherichia coli	155[a](25.4)[b]	231(32.4)	277(31.7)	261(38.2)	296(38.8)	362(39.3)	337(31.1)	267(35.7)	166(35.4)	2352(34.3)
Klebsiella pneumoniae	131(21.5)	90(12.6)	227(26)	122(17.9)	146(19.2)	208(22.6)	359(33.1)	209(28)	118(25.1)	1610(23.3)
Enterobacter cloacae	20(3.3)	38(5.3)	39(4.5)	45(6.6)	54(7.1)	40(4.3)	61(5.6)	39(5.2)	25(5.3)	361(5.3)
Acinetobacter baumannii	92(15.1)	96(13.5)	120(13.7)	70(10.2)	65(8.5)	67(7.3)	113(10.4)	89(11.9)	48(10.2)	760(11.1)
Pseudomonas aeruginosa	52(8.5)	94(13.2)	51(5.8)	49(7.2)	68(8.9)	72(7.8)	65(5.9)	40(5.4)	35(7.4)	526(7.7)
others	160(26.2)	164(23)	160(18.3)	136(19.9)	133(17.5)	173(18.7)	151(13.9)	103(13.8)	78(16.6)	1258(18.3)

a: The bolded data indicates the total number
b:The percentage of that group

The overall incidence of gram-positive BSIs was 2.01 episodes per 10,00 admissions, and the rate changed from 2.30 to 2.55 episodes per 10,00 admissions(X^2 = 10.61, P = 0.157) over 9 years (2.30 in 2010, 1.70 in 2011, 2.16 in 2012, 2.19 in 2013, 2.29 in 2014, 2.33 in 2015, 2.31 in 2016, 2.51 in 2017, 2.55 in 2018). Respectively, the overall incidence in each year was no obvious change in the general ward(X^2 = 8.85, P = 0.264) and the intensive care unit (X^2 = 5.78, P = 0.565).

Demographic And Clinical Characteristics

A total of 6867 episodes of gram-negative BSIs occurred among 3199 patients over the 9 years. Demographics and clinical data were available for 2980 of these clinically relevent episodes, as shown in Table 2. The median age was 53 years old (95% CI 54–55%), and 1947 (65%, 95% CI 40–89%) patients were male. There was no certain relationship between the age distribution and the distribution of strains ($p > 0.05$). Malignancy was the most common comorbidity (27%), followed by hypertension (14%). Moreover, The gram-negative BSIs incidence was 16.6 patients per 10,00 in the ICU every year, and 2 patients per 10,00 in the general ward, in additional, the medicine ward was accounted for 66 percent and surgery ward for 34 percent in the general ward, and the distribution of these clinically-relevant episodes in ward were without statistically different from our study ($p > 0.05$). Central intravenous catheters were the most common predisposing factors (10%), followed by chemoradiotherapy (6%) and indwelling urinary catheters (5%).

Table 2

Demographic and clinical characteristics of patients with BSIs

	Escherichia coli (n=1240)	Klebsiella pneumoniae (n=647)	Enterobacter cloacae(n=148)	Acinetobacter baumannii(n=431)	Pseudomonas aeruginosa(n=514)	total (n=2980)	p-value
age	55(54-56)	56(55-58)	52(48-56)	55(53-57)	52(49-55)	53(54-55)	0.1237
male	712(57,46-67)	456(70,64-75)	98(66,64-67)	301(70,65-74)	380(74,69-78)	1947(65,40-89)	0.3264
female	528(43,32-53)	191(30,24-35)	46(31,29-32)	124(29,24-33)	134(26,21-30)	1023(34,9-58)	0.3914
Comorbidities							
Malignancy	392(32,21-42)	183(28,22-33)	52(35,33-36)	71(16,11-20)	92(18,13-22)	790(27,2-51)	0.0609
Trauma	23(2,0-3)	19(3,2-4)	4(3,1-4)	51(12,7-16)	31(6,1-10)	128(4,0-8)	0.3264
Hypertension	139(1,0-21)	108(17,11-22)	22(15,13-16)	64(15,10-19)	80(16,11-20)	413(14,7-21)	0.5471
Heart disease	107(9,0-10)	81(13,7-18)	20(14,12-15)	67(16,11-20)	52(10,5-14)	327(11,6-16)	0.5471
Diabetes mellitus	128(10,0-20)	69(11,5-16)	13(9,7-10)	36(8,3-12)	58(11,6-15)	304(10,5-15)	0.7249
Hematological disease	141(11,0-21)	49(8,2-13)	37(25,23-26)	25(6,1-10)	42(8,3-12)	294(10,5-15)	0.1987
Hospital Ward							
Medical	733(59,48-69)	412(64,58-69)	86(58,56-59)	337(78,73-82)	398(77,72-81)	1966(66,41-90)	0.3264
Surgical	507(41,30-51)	235(36,30-41)	62(42,40-43)	94(22,17-26)	116(23,18-27)	1014(34,9-58)	0.0609
ICU	75(6,0-12)	120(19,13-24)	13(9,7-10)	240(56,51-60)	162(32,27-36)	610(20,10-30)	0.5471
Predisposing factors							
central intravenous catheter	69(6,0-12)	66(10,4-15)	13(9,7-10)	50(12,7-16)	87(17,12-21)	285(10,5-15)	0.7249
indwelling urinary catheter	20(2,0-4)	29(4,0-8)	2(1,0-2)	33(8,3-12)	55(11,6-15)	139(5,2-8)	0.3076
Immunosuppressive	37(3,1-5)	21(3,0-6)	1(1,0-2)	10(2,0-4)	14(3,0-6)	83(3,0-6)	0.7249
chemoradiotherapy	104(8,7-9)	42(6,0-11)	10(7,5-8)	2(0,0-0)	35(7,2-11)	193(6,3-9)	0.6848
endotracheal intubation	12(1,0-2)	15(2,0-4)	1(1,0-2)	22(5,0-9)	36(7,2-11)	86(3,0-6)	0.5731
tracheostomy tube	7(1,2-2)	6(1,0-2)	0(0,0-0)	7(2,0-4)	15(3,0-6)	35(1,0-2)	0.3264
Significant isolates							
Nosocomial	878(71,60-81)	501(77,71-82)	120(81,79-82)	367(85,80-89)	420(82,77-86)	2286(77,52-98)	0.3264
Community acquired	362(29,18-39)	146(23,17-28)	28(19,17-20)	64(15,10-19)	94(18,13-22)	694(23,0-46)	0.6848

Antimicrobial Susceptibility And Outcomes

Antimicrobial resistance levels for the most common organisms of the gram-negative BSIs are shown in Table 3. *Escherichia coli* showed a high level of resistance to penicillin, ciprofloxacin and levofloxacin; the resistance of ESBLs-producing *Escherichia coli* to penicillin was 99.7% especially. *Escherichia coli* was susceptible to cephalosporin and carbapenems and the resistance of ESBLs-producing *Escherichia coli* to the most antibiotic was higher than non-ESBLs producing *Escherichia coli* but to carbapenems(0.7% VS 5.1%). The resistance of *Klebsiella pneumoniae* to penicillin was more than 90%, the rates of carbapenems resistance of ESBLs-producing *Klebsiella pneumoniae* and non-ESBLs producing *Klebsiella pneumoniae* were 32.8% (159/486) and 8.1% (13/161), respectively. *Enterobacter cloacae* that showed low resistance to piperacillin/tazobactam, gentamicin, levofloxacin and the fourth generation cephalosporin, and the rates of carbapenems resistance of *Enterobacter cloacae* only was 1.4%, but the rate of penicillins resistance was 71.3%. However, *Acinetobacter baumannii* had a high resistance rate in most of the antibiotics including carbapenems, only the rate of levofloxacin resistance was less than 50%. *Pseudomonas aeruginosa* showed high sensitivity to piperacillin/tazobactam, quinolones, cephalosporins and carbapenems, the drug resistance rate is about 20%. In addition, since there is no national standard of the National Committee for Clinical Laboratory (NCCLS), it was not possible to judge the drug susceptibility of others gram-negative bacterial in the present study.

Table 3

Rates of antimicrobial resistance among gram-negative bacteria most frequently isolated from patients with BSIs

	Antimicrobial drug nri/nrt(%resistant)							
Microbiology	Penicillins	Piperacillin/tazobactam	Gentamicin	Ciprofloxacin	Levofloxacin	The third generation cephalosporin	The fourth generation cephalosporin	Carbape
Escherichia coli(ESBL-)	66.5%(356/536)	22.1%(118/536)	34.7%(186/536)	50.1% (269/536)	47.3%(254/536)	13.4%(72/536)	8.7%(47/536)	5.1%(27
Escherichia coli(ESBL+)	99.7%(702/704)	38.3%(270/704)	52.3%(368/704)	75.2% (529/704)	76.1%(536/704)	47.2%(332/704)	34.1%(240/704)	0.7%(5/
Klebsiella pneumoniae (ESBL-)	91.4%(444/486)	33.2%(161/486)	22.3%(108/486)	34.8% (169/486)	34.6%(168/486)	32.7%(159/486)	33.1%(161/486)	32.8%(1
Klebsiella pneumoniae (ESBL+)	99.6%(160/161)	51.8%(83/161)	31.5%(51/161)	49.2% (79/161)	48.7%(78/161)	58.9%(95/161)	36.7%(59/161)	8.1%(13
Enterobacter cloacae	71.3% (106/148)	11.8%(17/146)	15.3%(22/146)	-	5.2%(8/146)	31.6%(46/146)	3.8%(6/146)	1.4%(2/
Acinetobacter baumannii	-	74.5%(321/431)	-	78.3% (337/431)	47.5% (205/431)	76.5% (330/431)	75.1% (324/431)	73.3% (316/43
Pseudomonas aeruginosa	-	21.1%(/215)	-	18.3% (39/215)	22.8%(49/215)	19.2%(41/215)	16.2%(35/215)	27.8%(6

nri number of resistant isolates, nrt number of isolates tested
-: without resistant

The mortality of gram-negative bacterial bloodstream infections showed a downward trend from 2010 to 2018 (Fig. 1); The main pathogen causing death was *Acinetobacter baumannii* (27.7%), followed by *Escherichia coli* (26.5%), *Klebsiella pneumoniae*(24%), others(13.1%), *Pseudomonas aeruginosa* (6.5%) and *Enterobacter cloacae*(2.2%). Mortality in patients infected with *Klebsiella pneumoniae* (X^2 = 5.14, P = 0.643) and *Enterobacter cloacae* (X^2 = 38.78, P = 0.000) showed an increasing trend, while the mortality in patients infected with *Acinetobacter baumannii* (X^2 = 5.82, P = 0.562) and others (X^2 = 7.92, P = 0.339) shown a downward trend (Fig. 2). Between 2010 and 2018, the mortality in the ICU decreased from 27.03–14.93%(X^2 = 9.61, P = 0.212), while in the general ward fluctuated from 8.85–8.13% that without obvious decrease change(X^2 = 9.29, P = 0.232). (Fig. 3)

Discussion

In recent years, a shift of bacterial species from gram-positive to gram-negative bacteria as the causative agents of BSI was observed with a higher mortality in patients suffering from BSI[4, 15, 16, 17]. Neverthless, only few studies have focused on gram-negative bloodstream infections [18]. So our study examined the incidence and characteristics of gram-negative bloodstream infections in one of the largest tertiary-care hospitals in China and aimed to determine the antimicrobial susceptibility of the isolated pathogens against multiple antibiotics to achieve a clear outlook on the changing trend of their antibiotic susceptibility. According to our knowledge, thus far no such data about incidence rates of gram-negative BSIs based on large retrospective studies have been reported, most study have only reported on the distribution of the bacteria and the drug resistance.

In our 9-year study, the incidence of gram-negative BSIs switched order from 2.3 to 2.55 episodes per 10,00 admissions over 9 years. In the present study, there was no obvious change in overall incidence both in the ICU and on general ward per year. Nevertheless, many studies have reported a decrease in the incidence of gram-negative BSIs in general ward and ICU [19, 20, 21]. This might be explained with the incidence of gram-negative BSIs in our hospital was lower than other study[20] in china which has reported the incidence rate was 5.7/1000 admissions and our hospital is one of the largest general hospitals in China with more critically ill patients which means more invasive manipulation, more catheter indwelling, more comorbidity and other risk factors that lead to the occurrence of bloodstream infection.

BSIs are commonly associated with comorbidities, such as malignancies, diabetes mellitus and infections [22, 6]. In the present study, we found that malignancy was the most common comorbidity, and the major predisposing factor for BSIs was indwelling central intravenous catheters, this data was consistent with previous results [23, 24]. Several studies have reported that the second most common factors is abdominal and lower respiratory tract infections[25, 18]; while we found that chemoradiotherapy was the second most common predisposing factor for gram-negative BSIs. The observed differences might be due to the fact that the malignancy was the most common comorbidity with extensive use of central intravenous catheters for chemotherapy and the high rate of radiotherapy, which more commonly lead to BSIs.

The most common gram-negative bacterial species was *Escherichia* (34.3%), followed by *Klebsiella pneumoniae* (23.3%), these results was consistent with other studies[20, 26, 27]. In addition, 77% of infections were healthcare-associated while 23% were community-associated (77% VS 23%), but other studies have reported that gram-negative bacterial was more commonly the cause of community-associated[27]. We hypothesized that this occurred due to the following reasons: first, the study population was mainly focused on healthcare-associated infection and without outpatient, and blood collection and culturing was a routine examination for hospitalized patients with fever (T ≥ 38.5°C) in our hospital and the most blood was collected after admission with fever. Another reason was that the common predisposing factors of gram-negative BSIs such as central intravenous catheters, immunosuppression, and chemoradiotherapy were mainly found with hospitalized patients in our study. Furthermore, increasing use of medical technology in our hospital, the availability of life-saving treatments such as solid organ and hematopoietic stem cell transplantation, and improved intensive and supportive care have allowed for the survival of more severely ill patients, these patients who are extremely vulnerable to infection with healthcare-associated.

Escherichia coli showed a high level of resistance to penicillin, piperacillin/tazobactam, gentamicin, ciprofloxacin and Levofloxacin, the resistance of ESBLs-producing *Escherichia coli* to penicillin was 99.7% especially, these results were consistent with most studies[28, 29]. The reason might be ESBL was mainly transmitted between bacteria through plasmids, which can hydrolyze β-lactam antibiotics and carry resistance genes for aminoglycosides, quinolones and sulfonamides so that easily causing multiple drug resistance, and these plasmids frequently encode an inhibitor-resistant β-lactamase, namely OXA-1 which confers resistance to β-lactamase inhibitors including amoxicillin-clavulanate and piperacillintazobactam. *Escherichia coli* was susceptible to cephalosporin and carbapenems, but EARS-Net data indicated that in the EU mean resistance rate to the 3rd generation cephalosporins was 11.9%, ranging 4.4% in Sweden, 38.1% in Bulgaria, the ESBLs-producing *Escherichia coli* were reported between 71.5% and 100% in different European countries[30], the resistance rates were higher than our study especially for ESBLs-producing *Escherichia coli*. Carbapenem resistance in *E. coli* in Europe is rarely reported, the highest rates are found in Bulgaria (2.6%) and Turkey (4.0%) which was lower than our study, but our result was similar to a large multicenter surveillance study from China reported the prevalence of carbapenem resistant *E. coli* is 1.0%. In addition, the resistance of ESBLs-producing *Escherichia coli* to the most antibiotic was higher than non-ESBLs producing *Escherichia coli* but to carbapenems(0.7% VS 5.1%). Therefore, carbapenems may be considered as a first choice of treatment for BSI caused by *E. coli* and cephalosporin also as a good choice for BSI caused by non-ESBLs producing *Escherichia coli* especially the forth-generation cephalosporin.

The resistant rate of *Klebsiella pneumoniae* to penicillin was more than 90% and *Klebsiella pneumoniae* showed a moderate level of resistance to piperacillin/tazobactam, gentamicin, ciprofloxacin and Levofloxacin, to our knowledge, this is the first study which has reported such detailed results of resistance and be able to help guide the choice of antibiotics in clinical. The cephalosporin resistance rate of *Klebsiella pneumoniae* was similar to other Asia country[31] but be consistent with the studies done by Europe[32, 33] which have reported the resistance rate ranged between 2.7–88%, especially the ESBL positivity in these isolates were 65–100%. This may be explained with the species distribution and antimicrobial resistance that varies geographically. In addition, the carbapenems resistance rate of *Klebsiella pneumoniae* in our study was much higher than the most countries in the EU(2%)[32], this may be related to the unreasonable use of carbapenems in our hospital, which should arouse a great attention and vigilance the medical staff.

Enterobacter cloacae showed a high level of resistance to β-lactams such as penicillin(71.3%), but the resistance rate of the compound preparation is relatively good such as Piperacillin/tazobactam(11.8%). This difference may be due to the low expression of the AmpC enzyme gene through ECL with the high spontaneous mutagenicity leading to the emergence of drug-resistant strains. In addition, *Enterobacter cloacae* showed a good susceptibility to Gentamicin, Levofloxacin, the forth generation cephalosporin and Carbapenems but the three generation cephalosporin(31.6%), especially the resistant rate of Carbapenems was 1.4%. Therefore, it may be relatively easy to choose antibiotics in clinical. But it worth remembering that, although carbapenems and other antibiotics still maintain their high antibacterial activity, but carbapenem resistant strains have been reported to be on the rise[34] and rational use of antimicrobial agents to prevent the emergence of drug-resistant strains is still imminent.

Acinetobacter baumannii showed a high level of resistance to almost all antibiotics include carbapenems(73.3%), which was similarity to the results of the most studies from EU[35], while the resistant rate of carbapenems in Switzerland was 11%. Therefore, the treatment of *acinetobacter baumannii* resistant strains is still facing great difficulties, patients with *acinetobacter baumannii* bloodstream infections has accepted more invasive operation, mechanical ventilation, and a variety of history of antibiotic treatment after admission which has caused MDR bacterial infection with high mortality, clinician should pay more attention to identification the high-risk patients and began to activity treatment in time in order to reduce the risk of death. In addition, tigecycline and colistin maybe as a good choice for BSI caused by *Acinetobacter baumannii*, especially the resistance to colistin was rarely reported[36].

There was a good drug susceptibility to most antibiotics for *Pseudomonas aeruginosa* include Piperacillin/tazobactam, ciprofloxacin, levofloxacin, cephalosporin and carbapenems, almost all resistant rates was about 20% except the carbapenems(27.8%), the increasing resistant rate of carbapenems may be related to the wide application of carbapenems in clinic in recent years which has caused the metalloenzyme. Therefore, although the drug resistance of *pseudomonas aeruginosa* is optimistic at present, but attention still should be paid to the rational use of antibiotics and avoid exacerbating the resistance situation.

The crude mortality of gram-negative BSIs and the mortality of *Escherichia coli*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa* have shown a significant downward trend from 2010 to 2018. One possible reason might be that the number, correct timing and accuracy of blood cultures were all greater in a tertiary-care hospital thus medical workers could more correctly choose antibiotics in a timely manner and even choose a combination of cephalosporins and carbapenems to treatment infection in appropriately, and also as a reason to explain why *acinetobacter baumannii* bloodstream infection have a serious resistance situation but the mortality rate was reducing. Further, the use of high grade antibiotics such as carbapenems was restricted in non-tertiary hospitals. Another reason might be that tertiary-care hospitals have more complete strategy for strict control of infection that can reduce the mortality factors in BSIs. The mortality in the ICU has shown a decreased trend, while the general ward without obvious change, and the mortality was lower than other studies[37, 38, 39]. This could be explained by combinations regimens including at least 2 antibiotics have been associated with reduced mortality in comparison with the use of only one antibiotic, especially when the combination includes the carbapenems, which was used as a common treatment regimen in our ICU. Another important reason was the management of critically ill patients in the ICU that We optimize the antimicrobial doses and ways of administration according to the antibiotic instructions in order to achieve and maintain optimal plasmatic concentrations. besides, the diagnosis and treatment technologies of ICU such as ventilator and ECMO have been rapidly developing rapidly in our hospital over recent five years, and a variety of positive treatment measures have shown effective to improve cure rate and reduce mortality. Some other reasons that highlighted the importance of infection control measures among the medical staff of ICU are strict aseptic operations, good hand hygiene and similar. On the contrary, the mortality in the general ward without obvious change, the possible reason might be that the reason of bloodstream infection for the general ward was the use of indwelling central intravenous catheter because of chemotherapy and venous nutrition employed, while the main bacterial of these patients were gram-positive bacterial, and the incidence of gram-negative bacterial bloodstream infection was relatively low. In addition, the patients in general ward with lightly ill and the most of these patients were cured even if with the bloodstream infection thus maintain the mortality without obvious change.

There are several limitations in the present study that should be considered. First, the collection of clinical data depended on medical records rather than interviews and the comprehensive assessment of clinical symptoms. Second, there was an inevitable bias this was a single-centre study, and some of the results might have been affected by the small sample size. Finally, many drug susceptibility results could not be evaluated because of a lack of unified standards also and not all isolates underwent the same antimicrobial agent sensitivity tests, so many isolates lacked resistance comparisons with other isolates in the present study.

Conclusions

This study first clearly reported the epidemiology and microbiology of gram-negative bloodstream infections in a tertiary-care hospital in china. It demonstrates an increase in morbidity, while the mortality revealed the opposite trend especially in the ICU. Although the resistance rates to cephalosporins and carbapenems among the gram-negative BSIs increased, but these antibiotics are still considered the best treatment options for patients with gram-negative BSIs except Acinetobacter baumannii which shown a more severe situation of drug resistance. We expect our findings to help healthcare professionals to make informed decisions and provide better care for the patients, and hoped that more studies to update the relevant data of gram-negative bacteria bloodstream infection in time.

Abbreviations

BSIs
bloodstream infections
GNB
gram-negative bacteria
CHINET
China Antimicrobial Surveillance Network
PLAGH
Chinese People’s Liberation Army General Hospital
RT-NISS
The real-time nosocomial infection surveillance system
CLSI
The Clinical and Laboratory Standards Institute
NCCLS
National Committee for Clinical Laboratory
ICU
Intensive care unit
ECMO
Extracorporeal membrane oxygenation

Declarations

Availability of data and materials
The datasets generated during the current study are not publicly available to avoid violating the individual privacy of the patients, but they are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
The local institutional review board approved this study. For this type of study, formal consent is not required in our hospital.

Consent for publication
Not applicable

Ethics approval and consent to participate
The local institutional review board approved this study. For this type of study, formal consent is not required in our hospital.

Consent for publication
Not applicable

Competing interests
None of the authors declared conflicts of interest relevant to this article.

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Authors’ contributions
Zhixin Liang conceived of this study and was responsible for the manuscript. Qiang Zhu, Minghui Zhu collected the clinical data, interpreted the results, and wrote the manuscript. Chunyan Li, Lina Li, Mingxue Guo, Zhen Yang, Zhaorui Zhang participated in data collection and critical revision of the manuscript. All authors read and approved the final manuscript.

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Figures

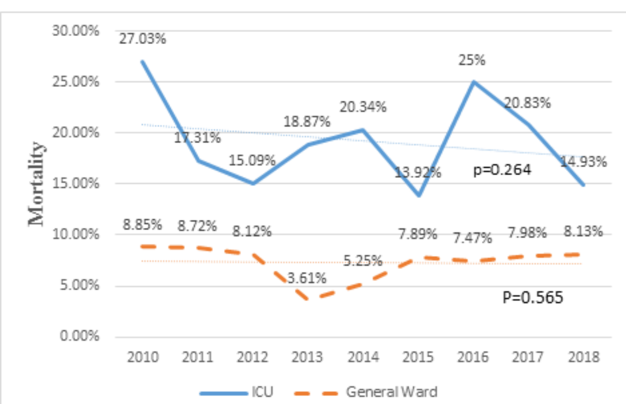

Figure 1

Mortality of BSIs due to ICU and General ward from 2010 to 2018

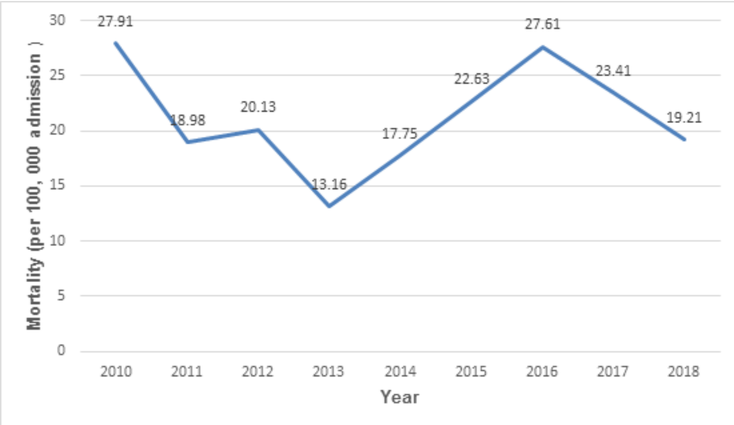

Figure 2

Mortality of the Gram-negative bacterials BSIs from 2010 to 2018. The mortality from Gram-negative BSIs shows downward trend; the rate fluctuated from 27.91 to 19.21 episodes per 100,000 admissions during the 9 years.

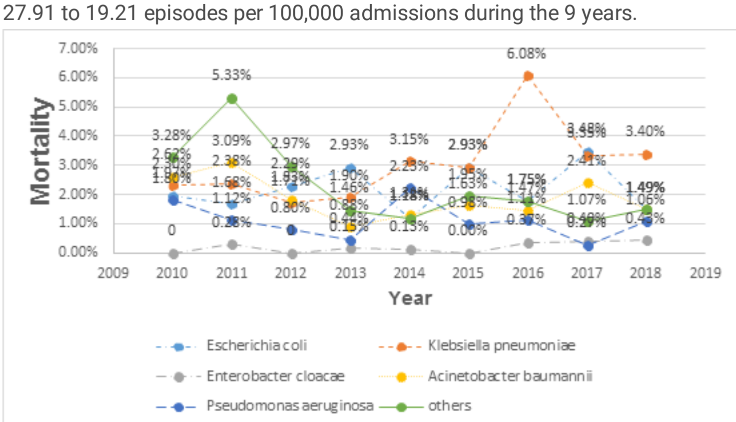

Figure 3

Mortality of the major gram-negattive bacterials BSIs from 2011 to 2018. Mortality in patients infected with Klebsiella pneumoniae (X2=5.14, P=0.643) and Enterobacter cloacae (X2=38.78, P=0.000) showed an increasing trend, while the mortality in patients infected with Acinetobacter baumannii (X2=5.82, P=0.562) and others (X2=7.92, P=0.339) shown a downward trend.