Journal of Critical Care 52 (2019) 92–96

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Epidemiological risk factors for nosocomial bloodstream infections: A four-year retrospective study in China

Zhao-qing Jiang [a], Shi-dong Wang [a], Dan-dan Feng [b], Bing-xin Zhang [c], Shi-hao Mao [b], Jian-nong Wu [b,*]

[a] First Clinical Medical College of Zhejiang Chinese Medical University, Hangzhou 310053, China
[b] Intensive Care Unit, First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, China
[c] First People's Hospital of Fuyang District, Hangzhou 311400, China

ARTICLE INFO

Keywords:
Nosocomial bloodstream infection
Microbiology
Risk factors
Venous catheter
Appropriate empirical therapy

ABSTRACT

Purpose: The objective of this study was to retrospectively research the clinical characteristics, pathogen distribution, prognosis of nosocomial bloodstream infection (nBSI), and the associated risk factors for nBSI.
Materials and methods: The clinical and microbiological data of patients with nBSI were retrospectively studied. Patients were treated at the First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Hangzhou, China) between January 2013 and December 2016.
Results: Our study spanned a four-year period and included 704 episodes of nBSI. The incidence rate was 4.11 per 1000 admissions. Of these cases, 96.7% were monomicrobial: gram-negative bacteria (56.4%), gram-positive bacteria (33.4%), and fungal (7%). Of all the *Escherichia coli* isolates, 41.5% were extended-spectrum β-lactamase-producing (ESBL)-positive. Of the *Klebsiella pneumoniae* isolates, 50.9% were resistant to imipenem. Of the *Staphylococcus aureus* isolates, 42.1% were methicillin-resistant. The overall 28-day mortality rate in all patients with nBSI was 24.4%. Parenteral nutrition (PN) and sequential organ failure assessment (SOFA) scores (≥5) were closely related to the 28-day mortality rate of nBSI, while removal of venous catheters and appropriate empirical therapy were protective factors of 28-day mortality.
Conclusions: Gram-negative bacteria predominantly developed in nBSI. Timely removal of venous catheters (catheter retention time ≥ 7 days) and implementation of appropriate empirical therapy improved the nBSI outcomes.

1. Introduction

Nosocomial bloodstream infection (nBSI) is a life-threatening condition that occurs in hospitalized patients. The incidence of bloodstream infection increases with extensive use of immunosuppressive therapy and invasive devices. There is an increasing burden as the number of cases of nBSI have increased [1,2], and the increased rate of nBSI is associated with high morbidity, mortality, and heavy financial costs [3].

The emergence and spread of antibiotic-resistant bacteria are of great concern. Due to increased antimicrobial drug resistance, treatment has become difficult, especially for infections caused by gram-negative organisms, which can be serious and even fatal in hospitalized patients [4,5]. Indeed, the increase in antimicrobial resistance has led to a pressing need to define species distribution and resistance patterns among nBSI-causing pathogens.

Therefore, hospital surveillance studies on nBSI can be useful for providing new insights. The incidence rate of nBSI from 2009 to 2011 at our hospital was 5.7 per 1000 hospital admissions [6]. With the reasonable use of antibiotics, implementation of hand hygiene, and ward environmental infection control measures over several years, we retrospectively analyzed the epidemiological characteristics, risk factors, and microorganism resistance patterns associated with the 28-day mortality of nBSI in recent years.

2. Materials and methods

2.1. Patients

Patients were included in the study if: 1) they had developed fever (>38 °C), chills, or hypotension after a hospital stay of >48 h; or 2) the same pathogenic organism was isolated from one or more blood cultures. Patients were excluded from the study if: 1) the duration of hospital stay was <48 h; 2) the first pathogen sample was not collected

* Corresponding author at: First Affiliated Hospital of Zhejiang Chinese Medical University, Youdian Rd 54, Hangzhou 310006, China.
E-mail address: 13777571598@163.com (J. Wu).

https://doi.org/10.1016/j.jcrc.2019.04.019
0883-9441/

within 24 h after either fever (>38 °C), chills, or hypotension; or 3) clinical data was incomplete.

2.2. Etiological data collection

Patients were treated at the First Affiliated Hospital of Zhejiang Chinese Medical University (Zhejiang Hangzhou, China) between January 2013 and December 2016. The primary clinical outcome was the 28-day mortality rate. Clinical information (age, gender, treatment, and prognosis) and microbiological data (classification and resistance) were recorded. Data were obtained from electronic medical records, and studies involving human or animal experiments conducted by any authors were not included. The Ethics Committee of our hospital approved the procedures, and the collected data were kept confidential.

2.3. Variables and definitions

Venous catheters include central venous catheters (CVC) and peripherally inserted central catheters. Poly-microbial nBSI was defined that >2 pathogens developed from the same specimen. All catheter-related bloodstream infections (CRBSI) were documented by quantitative tip culture. Both antibiotic-resistant and intermediately susceptible organisms were considered resistant based on calculated percentages of resistance. Multidrug resistance (MDR) refers to bacteria that are resistant to three or more types of antimicrobial drugs [7]. Extended-spectrum β-lactamase-producing (ESBL)-positive *Escherichia coli* and *Klebsiella pneumoniae* were defined as resistant or intermediately susceptible to third-generation cephalosporin. Carbapenem-resistant Enterobacteriaceae (CRE) refers to *E. coli, K. pneumoniae*, and *Enterobacter* sp. that are resistant or intermediately susceptible to carbapenems. Removal of venous catheters (catheter retention time ≥ 7 days) was defined as catheters that were removed after the diagnosis of nBSI. Empirical antibiotic therapy was considered appropriate when the antibiotic given during the first 48 h had *in vitro* activity against the causative organism.

2.4. Microbiological test

Two blood specimens were collected from each patient, and each specimen was cultured under aerobic and anaerobic conditions. Blood isolates were identified and antibiotic susceptibility testing was performed using the Vitek-2 microbial analyzer. Minimum inhibitory concentration breakpoints and quality control protocols were used according to the standards established by the Clinical and Laboratory Standards Institute.

2.5. Statistical analysis

Data were analyzed using IBM SPSS Statistics version 22. The results are expressed as the means ± standard deviation (SD) or median (IQR) for continuous variables, and as a proportion of the total number of patient or isolates for categorical variables. Differences in distributions between continuous variables were analyzed using the Student's *t*-test or the Kruskal-Wallis test. Categorical variables were analyzed using the Pearson's chi-square test or Fisher's exact test, as appropriate. Univariate analysis examined the association between predictor variables and risk of 28-day mortality. Variables that were statistically significant in the univariate analysis were included in a multiple logistic regression analysis to eliminate potential confounding factors. P values < 0.05 were considered statistically significant.

Table 1
Epidemiologic and demographic data of 704 patients with nBSI.

Parameter	Value[a]
Patient demographics	
Age (years)	67 ± 18
Male	431 (61.2%)
nBSI distribution[b]	
ICU	203 (28.8%)
Hematology	145 (20.1%)
Oncology	109 (15.5%)
Others	247 (35.1%)
Type of catheters	538 (76.4%)
Central venous catheter	368 (68.4%)
Peripherally inserted central catheter	170 (31.6%)
nBSI[c]	4.1‰ (704/171070)
CRBSI[d]	26.4% (186/704)
Organism	
Pure gram-negative	397 (56.4%)
Pure gram-positive	235 (33.4%)
Fungi	49 (7.0%)
Polymicrobial	23 (3.3%)
28-day mortality	172 (24.4%)

[a] Values are expressed as the number of patients (percentage), except age (mean ± SD).
[b] Department source of nosocomial bloodstream infection.
[c] Incidence rate per thousand hospital admissions in nBSI; between January 2013 and December 2016.
[d] Proportion of catheter-related bloodstream infections in nBSI.

3. Results

3.1. Study population and patient characteristics

Our study included 704 episodes of nBSI during the four-year study period. The overall incidence of nBSI was 4.1 episodes per 1000 admissions. The 28-day mortality rate for all patients was 24.4% (172/704). Patient characteristics and nBSI distribution are shown in Table 1.

3.2. Pathogen distribution

A total of 397 (56.4%) isolates were gram-negative, 235 (33.4%) were gram-positive, and 49 (7%) were fungi. Polymicrobial organisms accounted for 23 of 704 episodes (3.3%). The major pathogens were as follows, in the order listed: *E. coli* (19%), *K. pneumoniae* (17.1%), Coagulase-negative staphylococci (CoNS) (10.8%), *Enterococcus faecium* or *Enterococcus faecalis* (10.5%), and *Pseudomonas aeruginosa* (5.4%). CoNS isolates (n = 76) were characterized at the species level: *S. capitis* (31.6%), *S. haemolyticus* (21.1%), *S. epidermidis* (19.7%), and *S. hominis* (14.5%). In patients with monomicrobial nBSI, the mortality ranged from 10.5% (for *S. aureus*) to 34.8% (for *Candida*). The percentage of MDR strains among the deaths was >50% (Table 2).

Table 2
Distribution of the most frequently isolated pathogens causing nBSI and deaths.

Pathogen	No. of patients[a]	No. of deaths[b]	MDR rate of deaths
E. coli	134 (19.0%)	24 (18.0%)	23 (95.8%)
K. pneumoniae	120 (17.1%)	37 (30.8%)	35 (94.6%)
CoNS	76 (10.8%)	11 (14.5%)	10 (90.9%)
S. capitis	24 (3.4%)	6 (25.0%)	6 (100.0%)
S. haemolyticus	16 (2.3%)	0	0
S. epidermidis	15 (2.1%)	1 (6.7%)	1 (100.0)
S. hominis	11 (1.6%)	0	0
Others	27 (3.8%)	4 (14.8%)	3 (75.0%)
E. faecium/ E. faecalis	74 (10.5%)	23 (31.1%)	20 (87.0%)
P. aeruginosa	38 (5.4%)	11 (29.0%)	11 (100.0%)
S. aureus	38 (5.4%)	4 (10.5%)	2 (50.0%)
Candida	46 (6.5%)	16 (34.8%)	0
A. baumannii	36 (5.1%)	11 (30.6%)	11 (100.0%)

[a] Number of the most common pathogens associated with nBSI.
[b] Number of deaths from different pathogens.

Table 3
Rates of antimicrobial resistance among gram-negative bacteria most frequently isolated from patients with nBSI.

Antimicrobial	nri/nit (% resistant)			
Drug	*E. coli* (n = 134)	*K. pneumoniae* (n = 120)	*P. aeruginosa* (n = 38)	*A. baumannii* (n = 36)
Ampicillin-sulbactam	28/30 (93.3%)	29/30 (96.7%)	–	1/1 (100.0%)
Amikacin	23/132 (17.4%)	11/118 (9.3%)	7/38 (18.4%)	5/29 (17.2%)
Aztreonam	96/134 (71.6%)	74/118 (62.7%)	20/31 (64.5%)	26/26 (100.0%)
Cefepime	74/132 (56.1%)	63/119 (52.9%)	18/38 (47.4%)	31/36 (86.1%)
Ceftazidime	6/7 (85.7%)	5/7 (71.4%)	2/5 (40.0%)	2/2 (100.0%)
Ceftriaxone	84/132 (63.6%)	64/119 (53.8%)	31/38 (81.6%)	31/36 (86.1%)
Ciprofloxacin	90/131 (68.7%)	62/119 (52.1%)	13/38 (34.2%)	24/36 (66.7%)
Co-trimoxazole	71/129 (55.0%)	55/118 (46.6%)	38/38 (100.0%)	11/35 (31.4%)
ESBL-positive	54/130 (41.5%)	78/116 (67.2%)	–	–
Gentamicin	52/103 (50.5%)	33/95 (34.7%)	4/31 (12.9%)	18/32 (56.3%)
Imipenem	47/132 (35.6%)	60/118 (50.9%)	9/31 (29.0%)	15/26 (57.7%)
Levofloxacin	90/131 (68.7%)	63/119 (52.9%)	18/38 (47.4%)	24/36 (66.7%)

3.3. Antimicrobial susceptibility

Table 3 and Table 4 show the antimicrobial resistance levels of the most common nBSI-causing pathogens. Among the isolates, 41.5% of *E. coli* and 67.2% of *K. pneumonia* isolates were ESBL-positive. Among the gram-negative organisms, imipenem resistance was found in 50.9% of *K. pneumoniae* isolates, 57.7% of *Acinetobacter baumannii*, and 29% of *P. aeruginosa* isolates. Methicillin resistance was detected in 42.1% of *S. aureus* and in 13.9% of CoNS. In our study, gram-negative bacteria exhibited increased antimicrobial resistance, especially to imipenem. As resistance to imipenem generally results in MDR, this could explain why patients with MDR had higher mortality rates.

3.4. Clinical risk factors for 28-day mortality

Table 5 presents the results of the univariate analyses of 28-day mortality. A number of variables were significantly correlated with the 28-day mortality, including deep vein catheter indwelling, removal of venous catheter, parenteral nutrition (PN), appropriate empirical therapy, and sequential organ failure assessment (SOFA) scores (≥5). The results of the multivariate logistic regression analysis are presented in Table 6. After adjusting for potential confounding factors, we found that the PN (odds ratio (OR) = 2.490, $P < 0.001$) and SOFA scores (≥5) (OR = 3.803, $P < 0.001$) were strongly associated with 28-day mortality of nBSI, while removal of the venous catheter (OR = 0.346, $P < 0.001$) and appropriate empirical therapy (OR = 0.209, $P < 0.001$) were protective factors for 28-day mortality. As shown in our study, appropriate empirical therapy and timely removal of venous catheters were effective treatment strategies for nBSI.

4. Discussion

Nosocomial bloodstream infections (nBSI) are problematic in many general hospitals, as they are associated with high morbidity and mortality. In the face of increasing antimicrobial resistance, hospital surveillance studies focusing on nBSI have become important, and thus are providing the basis of empirical therapy. Therefore, we performed this study to collect data on defined infections rather than solely evaluating blood culture results.

The incidence rate of nBSI was 4.1 per 1000 hospital admissions in our study. In Canada, the incidence levels were 3.26 and 4.05 episodes per 1000 admissions in Calgary and Victoria, respectively [8]. In Switzerland, the incidence rate of nBSI increased from 211 in 2008 to 240 per 100,000 in 2014 [9]. However, the incidence rate in our study was not as high as that across the US (7.56 per 1000 admissions) [10] and lower than that (5.7 per 1000 admissions) between 2009 and 2011 in our hospital [6]. The reason for the decreased incidence of our hospital might be implementation of hand hygiene and ward environmental infection control measures, such as wiping a bed with a towel, eliminating repeated soaking, and standardizing the cleaning and disinfection process [11,12].

The bacterial distribution patterns in this study were consistent with those of prior reports [13-15]: gram-negative bacteria, followed by gram-positive bacteria and fungi. Bacteria belonging to Enterobacteriaceae are the primary sources of nBSI. Patients who have multiple organ dysfunction syndrome, chemotherapy, or radiotherapy, or those whose intestinal mucosal barrier dysfunction could result in bacterial translocation, are more susceptible to nBSI [16]; therefore, their intestinal mucosal barrier is a matter of concern. In addition, we found that *Candida* species rose from 4.6% [6] to 6.5%,

Table 4
Rates of antimicrobial resistance among Gram-positive bacteria most frequently isolated from patients with nBSI.

Antimicrobial	nri/nit (% resistant)		
Drug	CoNS (n = 76)	*E. faecium*/*E. faecalis* (n = 74)	*S. aureus* (n = 38)
Ampicillin-sulbactam	–	24/31 (77.4%)	–
Cefazolin	0/2 (0.0%)	10/11 (90.9%)	–
Ciprofloxacin	53/76 (69.7%)	61/74 (82.4%)	17/38 (44.7%)
Clindamycin	39/74 (52.7%)	55/62 (88.7%)	17/38 (44.7%)
Co-trimoxazole	29/76 (38.2%)	6/11 (54.6%)	2/38 (5.3%)
Erythromycin	59/74 (79.7%)	54/61 (88.5%)	19/38 (50.0%)
Gentamicin	29/57 (50.9%)	7/20 (35.0%)	5/31 (16.1%)
Levofloxacin	55/76 (72.4%)	59/73 (80.8%)	19/38 (50.0%)
Linezolid	24/57 (42.1%)	19/51 (37.3%)	11/33 (33.3%)
Methicillin	10/72 (13.9%)	0/1 (0.0%)	16/38 (42.1%)
Nitrofurantoin	5/76 (6.6%)	45/73 (61.6%)	3/38 (7.9%)
Penicillin	72/74 (97.3%)	51/62 (82.3%)	37/38 (97.4%)
Tetracycline	29/74 (39.2%)	31/62 (50.0%)	8/38 (21.1%)
Vancomycin	12/74 (16.2%)	14/63 (22.2%)	1/38 (2.6%)

Table 5
Univariate analysis of 28-day mortality in nBSI.

Risk factor	Adjusted odds ratio (95% CI)	P value
Gender (male)	1.167 (0.735–1.851)	0.513
Age (≥70 years)	1.046 (0.652–1.678)	0.852
Deep vein catheter indwelling	2.245 (1.400–3.600)	0.001
CRBSI	1.526 (0.908–2.565)	0.110
Catheter Retention time (≥30 d)	1.398 (0.891–2.192)	0.145
Removal of vein catheter	0.321 (0.177–0.582)	<0.001
PN	2.750 (1.662–4.549)	<0.001
Appropriate empirical therapy	0.241 (0.133–0.346)	<0.001
SOFA score (≥5)	2.572 (1.415–4.675)	0.002
△SOFA (≥2)	0.382 (0.116–1.252)	0.112
qSOFA (≥2)	1.678 (0.919–3.064)	0.092
MDR infection	0.881 (0.505–1.537)	0.655
MRSA	0.448 (0.043–4.652)	0.501
MRCNS	0.460 (0.046–4.591)	0.508
CRE infection	1.434 (0.857–2.400)	0.170

CRBSI – catheter-related bloodstream infection; PN - parenteral nutrition; SOFA - sequential organ failure assessment; qSOFA - quick sequential organ failure assessment; MRSA - methicillin-resistant *Staphylococcus aureus*; MRCNS - methicillin-resistant coagulase-negative staphylococci; MDR - multidrug resistant; CRE – carbapenem-resistant Enterobacteriaceae.

and *Candida* infections were shown in a previous study to be more prevalent in older patients [17].

Antibiotic resistance of gram-negative bacteria was prevalent in our study, especially in the case of *K. pneumoniae* and *A. baumannii*, with resistance to imipenem as high as 50%. A high percentage (>50%) of *Acinetobacter* isolates with resistance to carbapenems has been reported in southern Europe [18]. The prevalence of CRE, particularly in *K. pneumoniae*, has been detected in Greece, Italy, and Malta [19]. In 2014, The European Union/European Economic Area (EU/EEA) population-weighted mean in 7 of 29 reporting countries having methicillin-resistant *S. aureus* (MRSA) was >25% [18]. Antimicrobial resistance has progressively increased worldwide. Simultaneously, there has been increasing awareness regarding the damage that can occur with prolonged treatment with broad-spectrum antibiotics. Three important factors can influence antimicrobial choices: patient characteristics, risk factors of infection with specific pathogens, and severity of illness. Patient characteristics (antibiotic exposure) can influence the broadness of the initial antibiotic therapy. Invasive procedures increase the risk of colonization by MDR organisms. Of all the factors, illness severity may be the most important. Initial antimicrobial therapy diminishes with increased severity of illness, and this requires coverage against multiple patterns of bacterial resistance. Antimicrobial resistance has resulted in delays in the prescription of an effective antibiotic and high mortality rates [20]. This could explain why patients with *A. baumannii* (73.3%, 11/15) and *K. pneumoniae* (61.7%, 37/60) infections had higher mortality rates. Due to the complexity of the time required to test blood cultures, physicians usually opt for empirical therapy. Thus, we should pay more attention to local patterns of resistance and the local distribution of antibiotics.

The crude mortality rate observed in our study was 24.4%, which is higher than the 16.8% previously reported [6]. This discrepancy may be due to the incidence of severe and complicated diseases. Indeed, a large proportion of our patients had high SOFA scores and numerous concomitant diseases. The reported mortality of nBSI has remained high over the past decades, ranging between 20% and 30% [21,22]. The difference in mortality may depend on patient population and hospital circumstances.

Table 6
Multivariate logistic regression analysis of 28-day mortality in nBSI.

Risk factor	Adjusted odds ratio (95% CI)	P value
Removal of vein catheter	0.346 (0.207–0.578)	<0.001
PN	2.490 (1.537–4.035)	<0.001
Appropriate empirical therapy	0.209 (0.132–0.322)	<0.001
SOFA score (≥5)	3.803 (2.428–5.957)	<0.001

Our findings showed that SOFA scores (≥5) and PN were risk factors for the 28-day mortality of nBSI. The SOFA score is based on six factors and a marker of illness severity, which determines the extent or rate of organ dysfunction and predicts mortality [23]. SOFA scores (≥5) represent critical illness. In addition, PN provides an excellent environment for bacterial growth and reproduction. Vergara [24] reported that PN increases the risk of CRBSI, which increases with time. However, appropriate empirical therapy can protect patients from 28-day morality. The mortality rate was reduced by approximately 5× in patients receiving appropriate empirical therapy compared to those who did not (OR = 0.219, P < 0.001). We further validated this result in our study [6,25]. Therefore, efforts to increase the frequency of appropriate initial empirical therapy must be central to reduce the mortality associated with nBSI.

It is generally believed that nBSI is closely related to the application of a venous catheter. In our study, the use of deep vein catheters was as high as 76.4% (538/704). Bacteria can invade the blood through the catheter, consequently increasing the incidence of CRBSI. Bacteria in the blood that are displaced from the gut can easily adhere to the catheter and cause secondary infections, particularly intestinal tract infections. Antibacterial agents do not effectively destroy the pathogens that form biofilms within 4–5 days [26]. Thus, secondary infections are difficult to control. In our study, the main finding was decreased mortality in nBSI patients whose catheter was removed. The Infectious Diseases Society of America guideline recommends removing catheters [27]. When the antibacterial agent is ineffective and CRBSI is suspected, the catheter should be removed. However, whether catheters in nBSI patients should be removed early remains controversial. Nucci [28] reported that early catheter removal was not associated with any clinical benefit. Despite the lack of an evidence-based recommendation, the mortality associated with catheter removal is low [29,30]. Therefore, the timing of removal vein catheters may best be determined after carefully considering the risks and benefits to individual patients.

There are some limitations in our study. Our study was a retrospective research, and also was a single-center study. Accordingly, the sample size was limited and data collection was prone to selection bias, the guidelines for clinical treatment were limited. Therefore, expanding the scope of our research and improving early appropriate use of empirical antibiotics to reduce the mortality of nBSI should be implemented in our future study.

In conclusion, the incidence of nBSI was not very high in our study, and gram-negative bacteria were predominantly detected in nBSI. Removal of venous catheter, PN, appropriate empirical therapy, and SOFA scores (≥5) were associated with nBSI onset. Therefore, timely removal of venous catheters and implementation of appropriate empirical therapy improve the outcomes of nBSI.

Funding

This work were supported by the Medical Health Science and Technology Project of Zhejiang Provincial Health Commission (2A21602 (201602)), and (2013C33180), China.

Conflicts of interest statement

The authors report no conflicts of interest relevant to this article.

Acknowledgements

Zhao-qing Jiang especially wishes to thank her beloved parents, who have always believed that she can do it.

References

[1] Skogberg K, Lyytikäinen O, Ollgren J, et al. Population-based burden of bloodstream infections in Finland. Clin Microbiol Infect 2012;18(6) (E170-E6).
[2] de Kraker ME, Jarlier V, Monen JC, et al. The changing epidemiology of bacteraemias in Europe: trends from the European antimicrobial resistance surveillance system. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2013;19(9):860–8.
[3] MPH KSKM, Dror Marchaim MD, T-YCM MPH, et al. Effect of nosocomial bloodstream infections on mortality, length of stay, and hospital costs in older adults. J Am Geriatr Soc 2014;62(2):306–11.
[4] Hu FP, Guo Y, Zhu DM, et al. Resistance trends among clinical isolates in China reported from CHINET surveillance of bacterial resistance, 2005-2014. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis 2016;22(Suppl. 1):S9.
[5] Sofia M, Elpis M, Eirini MV, et al. A 5-year surveillance study on antimicrobial resistance of acinetobacter baumannii clinical isolates from a tertiary Greek hospital. Infect Chemother 2016;48(3):190–8.
[6] Wu J-n, Gan T-e, Zhu Y-x, et al. Epidemiology and microbiology of nosocomial bloodstream infections:analysis of 482 cases from a retrospective surveillance study. J Zhejiang Univ Sci B 2015:70–7 Biomedicine & Biotechnology). 1.
[7] Technical guidelines for prevention and control of multidrug-resistant hospital infection (Trial), J Adv Drug React 2011:108–9 02.
[8] Laupland KB, Kibsey PC, Gregson DB, et al. Population-based laboratory assessment of the burden of community-onset bloodstream infection in Victoria, Canada. Epidemiol Infect 2013;141(1):174–80.
[9] Buetti N, Atkinson A, Marschall J, et al. Incidence of bloodstream infections: a nationwide surveillance of acute care hospitals in Switzerland 2008–2014. BMJ Open 2017;7(3):e013665.
[10] Goto M, Al-Hasan MN. Overall burden of bloodstream infection and nosocomial bloodstream infection in North America and Europe. Clin Microbiol Infect 2013;19(6):501–9.
[11] Gan T, Hong X, Wu J, et al. Sequential enhanced cleaning eliminates multidrug-resistant organisms in general intensive care unit of a traditional Chinese medicine hospital. J Crit Care 2017;41:216–21.
[12] Zhu Y-x, Xuh Gan T-e, et al. The effect of enviromental cleaning on the MUltidrug-resistant organisms on high-touch surfaces in intensive care unit. Chin J Disinfect 2016;33(8):735–8.
[13] Hu FP, Zhu DM, Wang F, et al. CHINET 2014 surveillance of bacterial resistance in China. Chin J Infect Chemother 2015;15(5):401–10.
[14] Fupin HU, Guo Y, Zhu D, et al. CHINET surveillance of bacterial resistance across China:report of the results in 2016. Chin J Infect Chemother 2017;17(5):481–91.
[15] Fupin HU, Zhu D, Wang F, et al. Report of CHINET antimicrobial resistance surveillance program in 2015. Chin J Infect Chemother 2016;16(06):685–94.
[16] Zhang K, Jiao XF, Li JX, et al. Rhein inhibits lipopolysaccharide-induced intestinal injury during sepsis by blocking the toll-like receptor 4 nuclear factor-κB pathway. Mol Med Rep 2015;12(3):4415.
[17] Milazzo L, Peri AM, Mazzali C, et al. Candidaemia observed at a university hospital in Milan (northern Italy) and review of published studies from 2010 to 2014. Mycopathologia 2014;178(3–4):227–41.
[18] Karam G, Chastre J, Wilcox MH, et al. Antibiotic strategies in the era of multidrug resistance. Crit Care 2016;20(1):1–9.
[19] Grundmann H, Glasner C, Albiger B, et al. Occurrence of carbapenemase-producing Klebsiella pneumoniae and Escherichia coli in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. Lancet Infect Dis 2016;17(2):153–63.
[20] Ferrer R, Martinloeches I, Phillips G, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014;42(8):1749–55.
[21] Walaszek M, Rozanska A, Bulanda M, et al. Alarming results of nosocomial bloodstream infections surveillance in polish intensive care units. Przegl Epidemiol 2018;72(1):33–44.
[22] Schwab F, Geffers C, Behnke M, et al. ICU mortality following ICU-acquired primary bloodstream infections according to the type of pathogen: a prospective cohort study in 937 Germany ICUs (2006-2015). Plos One 2018;13(3):e0194210.
[23] Baradari AG, Firouzian A, Davanlou A, et al. Comparison of patients' admission, mean and highest sofa scores in prediction of ICU mortality: a prospective observational study. Materia Socio-Medica 2016;28(5):343–7.
[24] Vergara T, Veliz E, Fica A. Exposition to total parenteral nutrition increases the risk of catheter-related bloodstream infection. Revista Chilena de Infectologia 2016;33(6):603–8.
[25] Yamaga S, Shime N. Association between appropriate empiric antimicrobial therapy and mortality from bloodstream infections in the intensive care unit. J Infect Chemother 2017;24(4).
[26] Yousif A, Jamal MA, Raad I. Biofilm-based central line-associated bloodstream infections. Springer International Publishing; 2015; 157–79.
[27] Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the infectious diseases society of America. Clin Infect Dis 2009;vol. 49:1):1–45.
[28] Nucci M, Anaissie E, Betts RF, et al. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. Clin Infect Dis 2010;51(3):295–303.
[29] Marschall J, Piccirillo ML, Fraser VJ, et al. Catheter removal versus retention in the management of catheter-associated enterococcal bloodstream infections. Can J Infect Dis Med Microbiol 2013;24(3):e83–7.
[30] Tao F, Jiang R, Chen Y, et al. Risk factors for early onset of catheter-related bloodstream infection in an intensive care unit in China: a retrospective study. Med Sci Monit 2015;21:550–6.