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Retrospective analysis of hospital acquired linezolid-nonsusceptible enterococci infection in Chongqing, China, 2011-2014

Running title: LNSE infection among hospitalized patients

Xiaojiong Jia MS, Weijia Ma MS, Xiuyu Xu MD, Shuangshuang Yang MS, Liping Zhang MD, PhD*

Department of Laboratory Medicine, the First Affiliated Hospital of Chongqing Medical University, Chongqing, 400016, China

* Address correspondence to Liping Zhang, MD, PhD, Department of Laboratory Medicine. The First Affiliated Hospital Chongqing Medical University, No.1, Youyi Road, Yuzhong District, Chongqing, 400016, China. Phone: +86 023 89012756, Fax: +86 023 89012513.

E-mail addresses: 1309898173@qq.com (Liping Zhang).

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Abstract

Background: Linezolid-nonsusceptible enterococci (LNSE) is an increasingly emerging multidrug-resistant pathogen, and the caused nosocomial infections are difficult to manage. However, data on the host-related risk factors and clinical outcomes for LNSE infection are poorly characterized.

Methods: A retrospective case-case-control study of risk factors and clinical outcomes of hospitalized patients with LNSE infection during the period 2011-2014 was conducted in a teaching hospital in Chongqing, China. Case patients with LNSE and those with linezolid-susceptible enterococci (LSE), and controls with no enterococcal infection were compared at a ratio of 1:1:4. Two parallel multivariate logistic regression models were used to evaluate independent predictors for acquiring LNSE and LSE respectively.

Results: Forty-four LNSE cases, 44 LSE cases and 176 uninfected controls were analyzed. Multivariable analysis indicated that transferring from another hospital (odds ratio [OR], 3.57; 95% confidence interval [CI], 1.58-8.09), peripheral vascular disease (OR, 4.36; 95% CI, 1.64-11.60), and exposure to cephalosporins (OR, 4.24; 95% CI, 1.85-9.71) were unique independent predictors for acquiring LNSE. Gallbladder disease (OR, 3.64; 95% CI, 1.36-9.74) was independently associated with

LSE acquisition. Polymicrobial infection was the only factor identified in both LNSE and LSE groups compared to controls; however, no statistical significance was observed in in-hospital mortality.

Conclusion: Timely control efforts and appropriate antibiotic stewardship programs are necessary to effectively reduce the burden of LNSE infections among high-risk patients.

Keywords: Enterococci; epidemiology; infections; linezolid-nonsusceptible

Introduction

Linezolid, a synthetic oxazolidinone antibiotic that was approved for clinical practice in 2000, is available for the treatment of complicated infections and displays superb activity against a wide-range of clinically relevant gram-positive pathogens.¹ Linezolid inhibits bacterial growth by binding to the 50S ribosomal subunit and interfering with protein synthesis.² With the clinical utility of linezolid, an escalation of resistance has recently been discovered worldwide.³⁻⁴ In 2014, surveys reported by the Zyvox Annual Appraisal of Potency and Spectrum (ZAAPS) Program found linezolid nonsusceptible rates between 0.0% and 0.8% when testing against non-USA origin Gram-positive pathogens across nine consecutive years.³ Furthermore, similar results were obtained when observing the monitored species evaluated by the Linezolid Experience and Accurate Determination of Resistance (LEADER) Program in the USA from 2004-2012.⁴ Despite this, the rates have remained stable with no clear increase in recent years. The emergence of resistance is troubling and has created a need to explore risk factors of resistant pathogens. Several studies have analyzed risk factors caused by vancomycin-resistant Enterococcus (VRE) infection with reduced susceptibility to linezolid.⁵⁻⁹ However, few study has specifically assessed the risk factors associated with isolation of vancomycin-susceptible LNSE. In previous studies on vancomycin-resistant LNSE, the majority of these studies are subject to create biases by using traditional case-control designs,⁵⁻⁷ specially in overestimating the effect of antimicrobial exposure. Only two previous studies with the same topic have assessed risk factors by using case-case-control study design,⁸⁻⁹

but these studies have been limited by small sample size⁸ and absence of clinical outcomes⁹. The aim of our study was to identify specific variables associated with linezolid non-susceptible vancomycin-susceptible *Enterococcus* by using a case-case-control analysis. We also analyzed the outcomes of patients with LNSE infection compared to those of patients with LSE infection and those of uninfected controls. Additionally, the association between LNSE and LSE will be described in our study. Better understanding of these clinical predictors may reduce risks for patients with enterococcal infections and potentially facilitate early identification of high-risk patients, which could improve patient outcomes.

MATERIALS AND METHODS

Setting and design

A retrospective case-case-control study of risk factors for LNSE infection in hospitalized patients was conducted from January 2011 to December 2014 in the first affiliated hospital of Chongqing medical university, a major tertiary teaching hospital with 3,200 beds in southwest China. The hospital offers a full range of medical services, particularly with specialists in ophthalmology, hepatobiliary surgery, and neurosurgery.

We performed a retrospective case-case-control study in which the LNSE group and the LSE group were compared with the control group respectively to evaluate risk factors for the isolation of LNSE and LSE. Furthermore, we compared the LNSE

group with the LSE group to evaluate the potential risks specifically associated with isolation of LNSE.

The case-case-control design was used to explore risk factors for acquisition and spread of resistant pathogens more accurately than a common case-control study.¹⁰ The two case groups were defined as follows: the first case group consisted of patients with LNSE infections during hospitalization; the second case group consisted of patients with a positive clinical culture for LSE, based on a same-day culture and recovery from the site of infection. The control group was randomly selected from patients hospitalized during the same period of time with a 4:1 ratio to the case group, consisting of patients with other infections just not with Enterococci. Patients in all groups admitted for 48 hours or less were excluded and duplicate isolates were also excluded.

Time at risk was defined as the number of days from hospital admission up to the isolation of positive cultures for case patients. For uninfected controls, the total duration of hospital stay had to be at least as long as the time at risk of their matched case. The study was approved by the First Affiliated Hospital of Chongqing Medical University Biomedical Ethics Committee.

Microbiological analysis

A total of 44 LNSE isolates, including 39 *Enterococcus faecalis* (*E. faecalis*) and five *Enterococcus faecium* (*E. faecium*) isolates, were collected from January 2011 to December 2014. Bacteria were identified at the species level using the

VITEK2 Compact system (bioMérieux, France) or the VITEK MS system (bioMérieux, France). In vitro antimicrobial susceptibilities to 13 antimicrobial agents (clindamycin, ciprofloxacin, nitrofurantoin, moxifloxacin, quinupristin/dalfopristin, ampicillin, erythromycin, levofloxacin, tetracycline, vancomycin, linezolid, penicillin G, and tigecycline) were determined using a VITEK2 Compact AST-GP67 card (bioMérieux, France). All nonsusceptible results for linezolid were confirmed manually by standard broth microdilution method, as recommended by the Clinical and Laboratory Standards Institute (CLSI).¹¹ Enterococcal isolates with linezolid MICs ≥ 4 $\mu\text{g/mL}$ were classified as nonsusceptible. *Staphylococcus aureus* strain ATCC 29213 was used as a quality control stain during antimicrobial susceptibility testing and the results were interpreted using criteria based on the CLSI guidelines.¹²

Study population and characteristics

We analyzed data from patients' electronic medical records and clinical microbiology laboratory databases. Both infected and colonized patients were included in the study. Infection and colonization by LNSE or LSE were defined according to the clinical and laboratory criteria previously published reported by the Centers for Disease Control and Prevention.¹³ Cases and controls were compared using the following parameters as potential risk factors: (i) demographics (age and sex); (ii) presence of underlying conditions and comorbid conditions (diabetes mellitus, hypertension, lung disease, heart disease, hepatobiliary disease, gastrointestinal disease, renal disease and malignant disease); (iii) polymicrobial

infection (defined as the isolation of two or more bacterial or fungal species from the same sample); (iv) invasive procedures prior to a positive culture (receipt of total parenteral nutrition, mechanical ventilation, urinary catheter, drainage tube, central venous catheter, blood product transfusion and surgery); (v) exposure to antibiotics (received during hospitalization before a first positive culture was obtained); (vi) hospitalization history and outcome, including length of stay prior to positive culture, ICU admission, total length of hospital stay, in-hospital mortality, functional status deterioration (defined as deterioration from admission to discharge in 1 activity of daily living [ADL] according to Katz criteria)¹⁴, clinical success (defined as cure or improvement in signs and symptoms) and microbiological success (defined as elimination or presumed eradication of original pathogens during therapy or after the course of antibiotic therapy)¹⁵. We defined the time frame for risk at four weeks for invasive procedures and corticosteroids therapy, three months for ICU admission and antimicrobial exposure, and six months for surgery.

Statistical analysis

All analyses were performed by using SPSS v.21.0 software (SPSS Inc., Chicago, IL, USA). Univariate analyses were performed separately for each of the variables. Categorical variables were presented as frequencies and percentages, and were compared using McNemar's test. Continuous variables were presented as medians and interquartile ranges, and were compared by Student's T test (normally distributed variables) and the Wilcoxon rank-sum test (non-normally distributed variables). Odds

ratios (OR) and 95% confidence intervals (CI) were calculated to evaluate the strength of any association. Variables with $P < 0.10$ in the univariate analysis were included in the logistic regression model for the multivariable analysis. Forward selection processes were utilized to identify independent predictors. The final selected model was tested for confounding and collinearity. If a covariate affected the β -coefficient of a variable in the model by $>10\%$, then the confounding variable was maintained in the multivariate model. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit statistic. For all calculations, statistical significance was defined at $P < 0.05$ for two-tailed tests.

RESULTS

Overview

During the study period, 44 of 2,782 enterococcal isolates (1.6%) at our institution were identified to be LNSE. The 44 case patients were matched to 44 patients with LSE infection, and 176 patients without enterococcal infection serving as controls were randomly matched to LNSE or LSE cases at a 4:1 ratio. In total, 264 patients were in the final study cohort. Of the LNSE isolates included in the study, urine (19/44, 43.18%) was the most frequent sample. Furthermore, isolates were recovered from the following samples: wound secretion (8/44, 18.18%), bile (5/44, 11.36%), blood (4/44, 9.1%), intra-abdominal fluid (3/44, 6.82%), necrotic tissue (3/44, 6.82%), and cerebrospinal fluid (2/44, 4.55%). Of note, both case groups contained a higher proportion of patients who were admitted to the hepatobiliary unit

when compared with the control group (LNSE case group, 11.36%; LSE case group, 15.91%; control group, 4.55%, respectively). Demographics of patients including age, sex, and certain comorbid conditions were not significantly different (Table 1).

Analysis of LNSE infections vs Controls

The statistical results of the univariable and multivariable analysis for LNSE are listed in Tables 2 and 4, respectively. In the univariate analysis, LNSE acquisition was significantly more frequent in males, surgical units, and transfers from other hospitals. Cases with previous invasive devices were in general at significant risk, and each of the following invasive procedures during the four weeks prior to the isolation of LNSE increased the risk: mechanical ventilation, drainage tube, central venous catheter, blood product transfusion, and receipt of total parenteral nutrition. Among underlying diseases, patients with LNSE infection were more likely than uninfected controls to have gallbladder disease, renal disease, hypoalbuminaemia, hypokalemia, and peripheral vascular disease. In addition, a difference was noted in polymicrobial infections between cases and controls, which were more likely in patients with LNSE infection. When examining previous exposure to antibiotics, penicillin, cephalosporins and carbapenem were significantly associated with acquisition of LNSE.

In the multivariate analysis, transfer from another hospital (OR, 3.57; 95% CI, 1.58-8.09; P=0.002), peripheral vascular disease (OR, 4.36; 95% CI, 1.64-11.60; P=0.003), polymicrobial infection (OR, 4.47; 95% CI, 1.90-10.52; P=0.001), and

previous therapy with cephalosporins (OR, 4.24; 95% CI, 1.85-9.71; P=0.001) were independently associated with LNSE infection when compared with the uninfected controls.

Analysis of LSE infections vs Controls

With regard to the univariate analyses listed in Table 2, risk factors for LSE infection were found to be statistically significant in invasive procedures, including drainage tube, central venous catheter, blood product transfusion, and surgery during the prior six months. Investigations into underlying and comorbid conditions revealed a greater proportion of LSE cases with gallbladder disease, renal disease, peripheral vascular disease, severe anemia, and hypoalbuminaemia when compared to the uninfected control group. Additionally, polymicrobial infection was also significantly associated with the LSE case group. In contrast to LNSE cases, there was no significant difference in antibiotic exposures between LSE cases and controls.

Multivariate analysis for statistical data showed that gallbladder disease (OR, 3.64; 95% CI, 1.36-9.74; P=0.010) and polymicrobial infection (OR, 3.94; 95% CI, 1.73-8.97; P=0.001) were independent risk factors for LSE infection.

When comparing risk factors for LNSE and LSE with controls, we found that polymicrobial infection was similar in both infected groups. However, previous hospital transfer, peripheral vascular disease, and previous cephalosporins therapy were unique to the LNSE cohort. Furthermore, gallbladder disease was a unique risk factor for LSE cases. Hosmer-Lemeshow goodness-of-fit test results indicated that the

final LNSE or LSE acquisition models reflected the data well (Chi-square:4.283, P=0.509 and Chi-square:1.293, P=0.731, respectively).

Analysis of LNSE infections vs LSE infections

When the third model examining the LNSE and LSE were compared to evaluate the potential risks, heart disease, malignant disease, previous therapy with fluoroquinolone were statistically significant in the univariate analyses. We found heart disease (OR, 9.87; 95% CI, 1.84-52.82; P=0.007) , malignant disease (OR, 3.71; 95% CI, 1.32-10.42; P=0.013) and previous cephalosporins therapy (OR, 4.09; 95% CI, 1.39-12.03; P=0.021) as independent risk factors associated with the isolation of LNSE in the multivariate analysis. The model had a good calibration by the goodness-of-fit Hosmer and Lemeshow Test (Chi-square:2.885, P=0.823).

Clinical outcomes

Clinical outcomes are listed in Table 3. In the univariate analysis, factors associated with LNSE acquisition was significantly more frequent in functional status deterioration, admission to ICU in the past 3 months, postculture length of stay and total length of hospital stay. Postculture length of stay was found to be statistically significant in LSE cases. In addition, no differences between the groups were observed in clinical success or in microbiologic success. For in-hospital mortality, three (6.8%) patients infected with LNSE and two (4.5%) patients infected with LSE

died, with a mortality rate of uninfected controls at 1.7%. However, none of these variables remained significant when introduced into the multivariate model.

DISCUSSION

In the current study, we retrospectively analyzed the results from 4-year of surveillance data at a tertiary teaching hospital. This case-case-control study is the first analysis evaluating the clinical features, antibiotic exposure, and clinical outcomes for nosocomial patients with LNSE and LSE infections in China. Our main finding differed from previous studies, showing that patients transferred from another hospital was an independent risk factor for LNSE infection. Furthermore, another important finding from this study is that a high prevalence of gallbladder disease could be significantly associated with LSE infection.

In the present study, peripheral vascular disease was found to be independently predictive of LNSE infection, in line with previous observations by Pogue et al.⁹ Our data is useful in that we found transferring from another hospital was an independent predictor associated with the development of LNSE infection. To our knowledge, no other study reported an association between transferring from another hospital and LNSE infection that did reach the statistical significance. It is reasonable to posit that these patients are more likely to have a longer hospital stay, a lower recovery rate, and more severe clinical symptoms. These patients may have poor functional status, which places them at a higher risk for the development of infection. On the other hand, a majority of these patients might also have a higher frequency of exposure to

nosocomial pathogens via horizontal transmission in various hospital settings, and this may be associated with selective pressure of antibiotic exposure. Thus, these patients should be cared for with greater attention when designing infection control efforts and antibiotic treatment strategies.

Remarkably, polymicrobial infection was found to be significantly associated with both LNSE and LSE groups compared to controls. However, we found there was no significant difference between LNSE and LSE groups, demonstrating that polymicrobial infection was just associated with Enterococci infection in general. The most likely explanation for this finding, at least partially, is that the relatively high incidence of patients who had invasive procedures or inadequate treatment provides opportunities for the coexistence of organisms and increases the dissemination of nosocomial pathogens. On the other hand, we postulate that enterococcal infection in patients with relatively poor functional status could be more vulnerable to other bacterial infections. This alternative explanation is supported by experimental murine models of intraabdominal polymicrobial infection. When *Enterococcus* was implanted intraperitoneally in animals, it displayed relatively low virulence, whereas combinations with facultative or anaerobic organisms greatly enhanced virulence.¹⁶ Within polymicrobial infections, organisms often exhibit a synergistic effect that leads to enhanced persistence at the infected site, accelerated disease progression, and increased antimicrobial resistance.^{17, 18}

Of the factors associated with an increased risk for LSE, gallbladder disease is most notable. Our report showed a higher proportion of admission to the hepatobiliary

unit, especially in the LSE group. As is routinely recommended by clinical treatment guidelines, gallbladder disease should be treated using implanted medical devices, such as biliary drains and plastic stents,¹⁹ which may act as a nidus for bacterial adherence and biofilm formation, causing biliary sludge.^{19,20} Some bacteriological studies showed that patients with biliary sludge may be more likely to acquire a mixed infection primarily with enteric bacteria.¹⁹ Notably, *Enterococcus* has a relatively high isolation in biliary sludge, with the exception of gram-negative bacteria.²¹ Hence, it should be borne in mind that patients receiving implanted medical devices where gallbladder disease is diagnosed, enterococci should be considered as a potential pathogen when selecting empirical antibiotic therapy. Any decision should be based on the patient's clinical status and final microbiology results.

In contrast to previous studies, our study did not find an independent association between LNSE and previously linezolid exposure, possibly due to small sample size and limited statistical power. We found cephalosporins exposure were independently associated with the acquisition of LNSE. In our study, LNSE strains were isolated more frequently from patients treated with cephalosporins previously, especially for patients with a more severe underlying illness or those on long-term antibiotic therapy. Cephalosporins, with high-stability and safety, provide a broad-spectrum of antimicrobial activities and were widely applied in clinical practice. On the other hand, the mechanisms by which cephalosporins might influence LNSE acquisition have not been well established. However, a previous study by Pallares et al. presented that broad-spectrum antibiotics, with relatively little or no anti-enterococcal activity, could

produce a disruption in human bacterial flora and promote overgrowth of enterococcal species, particularly in the gastrointestinal tract.²² Selective pressure exerted by these agents could potentially increase the risk of intestinal colonization and accelerate the emergence of resistant enterococci, thus promoting the progression of these opportunistic pathogens.^{23, 24}

In the present study, we did not detect statistically significant difference in in-hospital mortality between LNSE group and control group. Similarly, no difference in in-hospital mortality was detected between LSE group and control group. Although mortality had a low incidence in our study, we cannot rule out the possibility that optimizing the choice of therapeutic strategies based on microbiological data may be beneficial to improving clinical outcomes. A meta-analysis with a total of 6,093 patients in 12 randomized controlled trials revealed that linezolid could improve clinical symptoms in 86.3% of patients, compared with 81.9% of patients with comparator antibacterials (glycopeptides and β -lactams).²⁵ Therefore, linezolid may effectively reduce the burden of Gram-positive bacterial infections.

Despite an attempt to maximize statistical efficiency and minimize potential bias, our study had several limitations. First, this retrospective report was conducted at a single medical center and our sample size was relatively small. Therefore, our findings might not be generalizable to other multicenter studies. Second, analysis of resistance at molecular level was not performed. Therefore, we could not confirm whether any LNSE outbreaks influenced our findings. Finally, our study found no statistical significance was observed in in-hospital mortality, probably due to that we

were not able to survey the conditions of discharged patients that may account for no difference in clinical outcomes.

CONCLUSIONS

In summary, this case-case-control study is conducted retrospectively to assess clinical predictors associated with LNSE or LSE infection. Our unique findings that associate transfer from another hospital with LNSE and gallbladder disease with LSE, could serve as an empiric and a preventive treatment standpoint for enterococcal infections. With the increase of enterococcal isolates and the severity of antibiotic resistance, the treatment of LNSE infections should be reassessed to predicate how to effectively control this emerging infection and how to optimally select therapeutic regimens to improve clinical outcomes during individualized treatment.

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Table 1. Demographic and clinical characteristics of patients.

Characteristic	LNSE (n=44)	LSE (n=44)	Controls (n=176)
Male sex, n (%)	25 (56.8)	22 (50)	63 (35.8)
Age, median (IQR), years	65 (50.0-79.0)	59 (35.5-73.0)	61 (49.0-74.0)
Unit of admission, n (%)			
Medical	12 (27.3)	15 (34.1)	79 (44.9)
Surgical	32 (72.7)	29 (65.9)	97 (55.1)
<i>Enterococcus</i> species, n (%)			
<i>E. faecalis</i>	39 (88.6)	31 (70.5)	–
<i>E. faecium</i>	5 (11.4)	13 (29.5)	–
Diabetes mellitus, n (%)	12 (27.3)	9 (20.5)	38 (21.6)
Hypertension, n (%)	14 (31.8)	7 (15.9)	49 (27.8)
Lung disease, n (%)	8 (18.2)	7 (15.9)	22 (12.5)
Heart disease, n (%)	10 (22.7)	2 (4.5)	25 (14.2)
Hepatobiliary disease, n (%)	12 (27.3)	15 (34.1)	17 (9.7)
Gastrointestinal disease, n (%)	12 (27.3)	12 (27.3)	34 (19.3)
Renal disease, n (%)	4 (9.1)	5 (11.4)	45 (25.6)
Malignant disease, n (%)	18 (40.9)	9 (20.5)	52 (29.5)
Postculture length of stay, median (IQR), days	7.5 (3.0-15.0)	5 (3.0-19.5)	4 (1.0-12.0)
Total length of hospital stay, median (IQR), days	37 (15.3-56.5)	22 (8.5-42.8)	17 (11.0-28.0)
In-hospital mortality, n (%)	3 (6.8)	2 (4.5)	3 (1.7)

Note: Data are number (%) of patients unless indicated otherwise. IQR, interquartile range; LNSE, linezolid-nonsusceptible enterococci; LSE, linezolid-susceptible enterococci.

Table 2

Univariate analysis of host-related risk factors for linezolid-nonsusceptible enterococci (LNSE) and linezolid-susceptible enterococci (LSE).

Risk factors	LNSE	LSE	Controls	LNSE vs Controls		LSE vs Controls		LNSE vs LSE	
	(n=44)	(n=44)	(n=176)	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
Male sex, n (%)	25 (56.8)	22 (50.0)	63 (35.8)	2.36 (1.21-4.62)	0.011	1.79 (0.92-3.49)	0.083	1.32(0.57-3.05)	0.521
Elderly (≥ 60 years), n (%)	25 (56.8)	22 (50.0)	95 (54.0)	1.12 (0.58-2.18)	0.735	0.85 (0.44-1.65)	0.636	1.32(0.57-3.05)	0.521
Surgical units, n (%)	32 (72.7)	29 (65.9)	97 (55.1)	2.17 (1.05-4.49)	0.034	1.58 (0.79-3.14)	0.195	1.38(0.56-3.43)	0.488
Transfer from another hospital, n (%)	22 (50.0)	14 (31.8)	34 (19.3)	4.18 (2.08-8.41)	<0.001	1.95 (0.93-4.07)	0.073	2.14(0.90-5.10)	0.083
Colonization, n (%)	11(25.0)	7(15.9)	20(11.4)	2.60(1.14-5.94)	0.020	1.48(0.58-3.75)	0.411	1.76(0.61-5.07)	0.290
Acute and chronic conditions on admission, n (%)									
Diabetes mellitus	12 (27.3)	9 (20.5)	38 (21.6)	1.36(0.64-2.90)	0.421	0.93(0.41-2.11)	0.869	1.46(0.54-3.92)	0.453
Hypertension	14 (31.8)	7 (15.9)	49 (27.8)	1.21(0.59-2.47)	0.602	0.49(0.21-1.17)	0.104	2.47(0.88-6.89)	0.080
Heart disease	10 (22.7)	2 (4.5)	25 (14.2)	1.78(0.78-4.04)	0.167	0.29(0.07-1.27)	0.081	2.69(1.04-6.94)	0.037
Malignant disease	18 (40.9)	9 (20.5)	52 (29.5)	1.65(0.83-3.27)	0.148	0.61(0.28-1.37)	0.228	6.18(1.27-30.11)	0.013

Respiratory failure	5 (11.4)	1 (2.3)	6 (3.4)	3.63 (1.06-12.51)	0.075	0.66 (0.08-5.62)	1.000	5.51(0.62-49.28)	0.091
Gallbladder disease	9 (20.5)	11(25)	15 (8.5)	2.76 (1.12—6.81)	0.045	3.58 (1.51-8.48)	0.002	0.77(0.28-2.10)	0.611
Renal disease	4 (9.1)	5 (11.4)	45 (25.6)	0.29 (0.1-0.86)	0.019	0.37 (0.14-1.01)	0.044	0.78(0.20-3.12)	0.725
Urinary tract infection	9 (20.5)	10 (22.7)	59 (33.5)	0.51 (0.23-1.13)	0.093	0.58 (0.27-1.26)	0.167	0.87(0.32-2.42)	0.796
Peripheral vascular disease	13 (29.5)	9 (20.5)	18 (10.2)	3.68 (1.64-8.28)	0.001	2.26 (0.94-5.44)	0.064	1.63(0.61-4.34)	0.330
Severe anemia*	4 (9.1)	7 (15.9)	8 (4.5)	2.1 (0.60-7.32)	0.414	3.97 (1.36-11.64)	0.019	0.53(0.,14-1.95)	0.334
Hypoalbuminaemia*	23 (52.3)	25 (56.8)	63 (35.8)	1.96 (1.01-3.83)	0.045	2.36 (1.21-4.62)	0.011	0.83(0.36-1.93)	0.670
Hypokalemia*	15 (34.1)	12 (27.3)	30 (17.0)	2.52 (1.21-5.26)	0.012	1.83 (0.84-3.95)	0.123	1.38(0.56-3.43)	0.490
Neutropenia*	7 (15.9)	6 (13.6)	13 (7.4)	2.37 (0.89-6.36)	0.143	1.98 (0.71-5.54)	0.308	1.20(0.37-3.90)	0.764
Corticosteroids within 4 weeks	7 (15.9)	8 (18.2)	25 (14.2)	1.14 (0.46-2.84)	0.774	1.34 (0.56-3.22)	0.509	0.85(0.28-2.59)	0.780
Polymicrobial infection	19 (43.2)	16 (36.4)	19 (10.8)	6.28 (2.93-13.47)	<0.001	4.72 (2.17-10.27)	<0.001	1.33(0.57-3.13)	0.513
Invasive procedures within prior 4 weeks, n (%)									
Receipt of total parenteral nutrition	4 (9.1)	3 (6.8)	3 (1.7)	5.77 (1.24-26.79)	0.044	4.22 (0.82-21.67)	0.179	1.37(0.29-6.50)	1.000
Mechanical ventilation	10 (22.7)	8 (18.2)	15 (8.5)	3.16 (1.31-7.62)	0.008	2.39 (0.94-6.05)	0.110	1.32(0.47-3.75)	0.597

Urinary catheter	28 (63.6)	27 (61.4)	85 (48.3)	1.87 (0.95-3.70)	0.069	1.7 (0.87-3.34)	0.121	1.10(0.47-2.61)	0.826
Drainage tube	21 (47.7)	22 (50.0)	51 (29.0)	2.24 (1.14-3.40)	0.018	2.45 (1.25-4.81)	0.008	0.91(0.40-2.11)	0.831
Central venous catheter	16 (36.4)	12 (27.3)	25 (14.2)	3.45 (1.64-7.28)	0.001	2.27 (1.03-4.98)	0.038	1.52(0.62-3.76)	0.360
Blood product transfusion	13 (29.5)	12 (27.3)	23 (13.1)	2.79 (1.28-6.10)	0.008	2.5 (1.13-5.53)	0.021	1.12(0.44-2.83)	0.813
Surgery in the past 6 months	28 (63.6)	29 (65.9)	79 (44.9)	2.15 (1.09-4.25)	0.026	2.37 (1.19-4.74)	0.013	0.91(0.38-2.17)	0.823
Antimicrobial exposure within 3 months, n (%)									
Penicillin	14(31.8)	10(22.7)	31(17.6)	2.18(1.04-4.59)	0.037	1.38(0.62-3.08)	0.436	1.59(0.62-4.10)	0.338
Cephalosporins	29 (65.9)	20 (45.5)	49 (27.8)	5.01 (2.48-10.14)	<0.001	2.16 (1.10-4.26)	0.024	2.32(0.98-5.49)	0.053
Aminoglycosides	7 (15.9)	5 (11.4)	18 (10.2)	1.66 (0.65-4.27)	0.288	1.13 (0.39-3.22)	1.000	1.48(0.43-5.06)	0.534
Fluoroquinolone	11 (25.0)	3 (6.8)	28 (15.9)	1.76 (0.80-3.89)	0.158	0.39 (0.11-1.34)	0.121	4.56(1.17-17.69)	0.020
Macrolides	2 (4.5)	0 (0)	1 (0.6)	8.33 (0.74-94.09)	0.191	0.99 (0.98-1.01)	1.000	1.05(0.98-1.12)	0.474
Tigecycline	0 (0)	0 (0)	1 (0.6)	0.99 (0.98-1.01)	1.000	0.99 (0.98-1.01)	1.000	NA	NA
Carbapenem	11 (25.0)	6 (13.6)	13 (7.4)	4.18 (1.72-10.14)	0.002	1.98 (0.71-5.54)	0.308	2.11(0.70-6.33)	0.177
Metronidazole	19 (43.2)	11 (25.0)	54 (30.7)	1.72 (0.87-3.38)	0.115	0.75 (0.35-1.60)	0.460	2.28(0.921-5.64)	0.072

Vancomycin	6 (13.6)	6 (13.6)	9 (5.1)	2.93 (0.98-8.73)	0.095	2.93 (0.98-8.73)	0.095	1.00(0.30-3.38)	1.000
Linezolid	6 (13.6)	3 (6.8)	4 (2.3)	6.79 (1.83-25.24)	0.005	3.15 (0.68-14.61)	0.291	2.16(0.50-9.24)	0.291

Note: Data are no. (%) unless otherwise indicated. Bold face indicate values that are significant ($P < 0.05$). OR, odds ratio; CI, confidence interval; NA, data not available.

* Severe anemia (hemoglobin < 60g/L), hypoproteinemia (serum total protein < 60g/L or albumin < 25g/L), hypokalemia (Serum potassium < 3.5mmol/L) and neutropenia (absolute neutrophil count < 500 cells/ μ L).

Table 3**Univariate analysis of LNSE and LSE infections for outcomes.**

Outcomes	LNSE	LSE	Controls	LNSE vs Controls		LSE vs Controls		LNSE vs LSE	
	(n=44)	(n=44)	(n=176)	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
In-hospital mortality, n (%)	3 (6.8)	2 (4.5)	3 (1.7)	4.22(0.82-21.67)	0.179	2.75(0.45-16.96)	0.572	1.54(0.24-9.68)	1.000
Functional status deterioration, n (%)	11(25.0)	6 (13.6)	16 (9.1)	3.33(1.42-7.83)	0.004	1.58(0.58-4.30)	0.537	2.11(0.70-6.33)	0.177
Clinical success	23(52.3)	29(65.9)	111(63.1)	0.64(0.33-1.25)	0.189	1.13(0.57-2.27)	0.726	0.57(0.24-1.34)	0.193
Microbiologic success	20(45.5)	27(61.4)	103(58.5)	0.59(0.30-1.15)	0.118	1.13(0.57-2.22)	0.732	0.53(0.23-1.23)	0.135
Admission to ICU in the past 3 months, n (%)	18 (40.9)	11 (25.0)	40 (22.7)	2.35(1.17-4.73)	0.014	1.13(0.53-2.44)	0.749	2.08(0.84-5.16)	0.112
Postculture length of stay, median (IQR), days	7.5 (3.0-15.0)	5 (3.0-19.5)	4 (1.0-12.0)	NA	0.011	NA	0.030	NA	0.318
Total length of hospital stay, median (IQR), days	37 (15.3-56.5)	22 (8.5-42.8)	17 (11.0-28.0)	NA	0.001	NA	0.134	NA	0.426

Note: Bold face indicate values that are significant ($P < 0.05$). ICU, intensive-care unit; IQR, interquartile range; NA, data not available.

Table 4**Multivariate analysis of host-related risk factors and clinical outcomes for LNSE and LSE.**

Variable	95% CI	OR	P value
LNSE vs Controls			
Transfer from another hospital	1.58-8.09	3.57	0.002
Peripheral vascular disease	1.64-11.60	4.36	0.003
Polymicrobial infection	1.90-10.52	4.47	0.001
Cephalosporins exposure within three months	1.85-9.71	4.24	0.001
LSE vs Controls			
Gallbladder disease	1.36-9.74	3.64	0.010
Polymicrobial infection	1.73-8.97	3.94	0.001
LNSE vs LSE			
Heart disease	1.84-52.82	9.87	0.007
Malignant disease	1.32-10.42	3.71	0.013
Cephalosporins exposure within three months	1.39-12.03	4.09	0.021

Note: Bold face indicate values that are significant ($P < 0.05$). OR, odds ratio; CI, confidence interval.