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ORIGINAL ARTICLE

Outcomes and characteristics of ertapenem-nonsusceptible *Klebsiella pneumoniae* bacteremia at a university hospital in Northern Taiwan: A matched case-control study

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KEYWORDS
Bacteremia;
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Background and purpose: Carbapenem-resistant *Klebsiella pneumoniae* is an emerging problem worldwide. The object of this study was to investigate the risk factors, characteristics and outcomes of ertapenem-nonsusceptible *K pneumoniae* (ENSKp) bacteremia.

Methods: We conducted a 1:2 ratio matched case-control study. The controls were randomly selected among patients with ertapenem-susceptible *K pneumoniae* (ESKp) bacteremia and were matched with ENSKp cases for bacteremia.

Results: Seventy-five patients were included in this study (25 cases and 50 controls). Bivariate analysis showed that prior exposure to either β-Lactam/β-Lactam-lactamase inhibitors ($p = 0.008$) or 4th generation cephalosporins ($p < 0.001$), chronic obstructive pulmonary disease (COPD) ($p = 0.001$), acute renal failure ($p = 0.021$), chronic kidney disease without dialysis ($p = 0.021$), recent hospital stay ($p = 0.016$), intensive care unit stay ($p = 0.002$), mechanical ventilation ($p = 0.003$), central venous catheter placement ($p = 0.016$), Foley indwelling ($p = 0.022$), polymicrobial bacteremia ($p = 0.003$) and higher Pittsburgh bacteremia score ($p < 0.001$) were associated with ENSKp bacteremia. The multivariate analysis showed that prior exposure to 4th generation cephalosporins (odds ratio [OR], 28.05; 95% confidence interval [CI], 2.92—269.85; $p = 0.004$), COPD (OR, 21.38; 95% CI, 2.95—154.92; $p = 0.002$) and higher Pittsburgh bacteremia score (OR, 1.35; 95% CI, 1.10—1.66;

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$p = 0.004$) were independent factors for ENSKp bacteremia. ENSKp bacteremia had a higher 14-day mortality rate than ESKp bacteremia (44.0% vs. 22.0%; $p = 0.049$). The overall in-hospital mortality rates for these two groups were 60.0% and 40.0% respectively ($p = 0.102$). *Conclusion:* ENSKp bacteremia had a poor outcome and the risk factors were prior exposure of 4th generation cephalosporins, COPD and higher Pittsburgh bacteremia score. Antibiotic stewardship may be the solution for the preventive strategy.

Introduction

Klebsiella pneumoniae has caused worldwide concern because of its ability to produce extended-spectrum β-lactamases (ESBLs). Carbapenems have been the choice for the management of infections caused by ESBL-producing *K pneumoniae*.[1] Carbapenem resistance in *K pneumoniae* was first reported a decade ago[2] and have emerged in several countries subsequently.[3,4]

The production of carbapenem resistance in *K pneumoniae* is attributed to several mechanisms, including high-level production of an AmpC β-lactamase combined with loss of outer membrane proteins or, rarely, efficient carbapenem-hydrolyzing β-lactamases (e.g., the metallo-β-lactamases in class B by the Ambler classification).[5] However, a plasmid-mediated class A carbapenem-hydrolyzingβ-lactamase, *K pneumoniae* carbapenemase (KPC) type-1, was first described in 2001 in an isolate of *K pneumoniae* from a hospital in North Carolina, USA.[6] Subsequently, the novel enzyme family, KPC, was generally described in the USA and has caused outbreaks since 2003, primarily in New York.[5,7–9] An outbreak of bacteremia due to a strain of carbapenem-resistant *K pneumoniae* (CRKp) was reported in Israeli hospitals in recent years.[10–12] The emergence of a new antibiotic resistance mechanism by New Delhi metallo-β-lactamase-1 in India, Pakistan, and the United Kingdom in 2010 has caused worldwide concern.[13]

The emergence and spread of carbapenem-nonsusceptible (intermediately resistant or resistant) *K pneumoniae* is becoming a major global health problem and a clinical challenge for physicians.[14] Although risk factors for CRKp infection have been reported by several investigators,[12,15–19] there were limited observations that focused on bloodstream infection, which may lead to a higher mortality rate and poor outcome. Therefore, we performed a matched case-control study to investigate potential risk factors for the development of ertapenem-nonsusceptible *K pneumoniae* (ENSKp) bacteremia and the associated clinical outcomes.

Materials and methods

Study design and patients

We conducted this study at the Chang-Gung Memorial Hospital, Linkou Medical Center, a 3715-bed tertiary-care general hospital in Northern Taiwan. We reviewed the blood culture records at the microbiology laboratory databases to identify the bacteremia caused by ENSKp between January 2007 and December 2009. The medical records of patients with ENSKp bacteremia were reviewed. The clinical characteristics of these patients was obtained, including age, gender, dates of hospital admission, dates of blood cultures and dates of mortality or discharge. For patients with more than one episode of bloodstream infection of *K pneumoniae*, only data relevant to the first episode were collected and analyzed. Various risk factors were taken into the analysis only if they had occurred before the development of the infection. Variables analyzed as risk factors are summarized in Table 1, including: comorbidities; recent hospitalization (≦ 14 days, including nursing home or outside hospital transferring) and surgery (during this admission and before the bacteremia); intensive care unit (ICU) stay; mechanical ventilation usage; placement of a central venous catheter; Foley indwelling; existence of tracheotomy, colostomy or gastrostomy; implantation of prosthesis; polymicrobial pathogens isolated with *K pneumoniae* from blood concurrently; the Pittsburgh bacteremia score for disease severity;[20] and previous exposure to various antimicrobials. Exposure to a specific antimicrobial agent was considered significant and included in our analysis only if: (1) the antibiotic had been administered for at least 3 consecutive days; and (2) that exposure had occurred within 30 days before the development of bacteremia.

Selection of controls

For each patient with ENSKp bacteremia, we randomly selected two matched control patients with ertapenem-susceptible *K pneumoniae* (ESKp) bacteremia from the database. We used a stepwise matching method to identify the appropriate control patients matched to a case for the same gender, age ±8 years, the same year of hospital admission and length of hospital stay up to isolation of *K pneumoniae* ±5 days.

Microbiologic analysis

Blood cultures were processed in the clinical microbiology laboratory, using the automated blood culture system (BACTEC 9240 system; Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). The isolated organisms that grew on the culture were identified according to routine bacteriological procedures. Antibiotic susceptibility testing was determined by the disk diffusion method in

Table 1 Clinical characteristics of 75 patients with bacteremia caused by *Klebsiella pneumoniae* with and without the ertapenem-nonsusceptible phenotype

Characteristics	Ertapenem-nonsusceptible group (n = 25)	Ertapenem-susceptible group (n = 50)	p
	Mean ± SD or No. (%)	Mean ± SD or No. (%)	
Demographic			
Gender (Male)	16 (64.0%)	32 (64.0%)	1.000
Age	64.9 ± 16.0 (19–89)	64.9 ± 15.4 (14–90)	0.998
Length of hospital stay (d)	46.8 ± 26.2 (4–93)	54.4 ± 41.8 (8–219)	0.411
Duration before bacteremia (d)	27.7 ± 23.2 (0–76)	27.3 ± 22.6 (0–81)	0.946
Comorbidities			
Heart diseases[a]	6 (24.0%)	10 (20.0%)	0.690
Malignancies (including hematologic malignancy)	9 (36.0%)	28 (56.0%)	0.102
COPD	8 (32.0%)	2 (4.0%)	0.001*
Acute renal failure	12 (48.0%)	11 (22.0%)	0.021*
Chronic kidney disease without H/D	7 (28.0%)	4 (8.0%)	0.021*
Uremia with regular dialysis	1 (4.0%)	4 (8.0%)	0.513
Diabetes mellitus	9 (36.0%)	19 (38.0%)	0.866
Chronic liver diseases[b]	6 (24.0%)	11 (22.0%)	0.845
Neurologic diseases	10 (40.0%)	13 (26.0%)	0.215
Immunosuppressant use[c]	8 (32.0%)	9 (18.0%)	0.172
Previous transplantations	0	0	not available
Admission to the hospital (< 14 d)	11 (44.0%)	9 (18.0%)	0.016*
Intensive care unit stay	18 (72.0%)	17 (34.0%)	0.002*
Mechanical ventilation support	18 (72.0%)	18 (36.0%)	0.003*
Polymicrobial bacteremia	9 (36.0%)	4 (8.0%)	0.003*
Pittsburgh bacteremia score	6.00 ± 3.39 (0–13)	2.98 ± 2.81 (0–12)	<0.001*
Invasive procedure or devices			
Central venous catheters	21 (84.0%)	28 (56.0%)	0.016*
Foley indwelling	17 (68.0%)	20 (40.0%)	0.022*
Surgery during this admission	2 (8.0%)	16 (32.0%)	0.022*
Prosthesis placement	4 (16.0%)	5 (10.0%)	0.451
Colostomy/gastrostomy	1 (4.0%)	3 (6.0%)	0.716
Tracheostomy	3 (12.0%)	5 (10.0%)	0.791
Prior antibiotic exposure (≧3 days within 30 days), including range and average days of antibiotics usage			
β-Lactams (Penicillin/Ampicillin/ Amoxicillin/Oxacillin/Piperacillin)	3 (12.0%) (6-12, 9.3 days)	4 (8.0%) (5–14, 7.5 days)	0.575
β-Lactam-lactamase inhibitors[d]	8 (32.0%) (5–15, 10.4 days)	4 (8.0%) (4–12, 8.3 days)	0.008*
1st & 2nd generation cephalosporins	1 (4.0%) (12, 12.0 day)	8 (16.0%) (7–22, 11.8 days)	0.132
3rd generation cephalosporins	12 (48.0%) (4–22, 9.2 days)	17 (34.0%) (4–23, 11.3 days)	0.241
4th generation cephalosporins	10 (40.0%) (4–27, 9.3 days)	1 (2.0%) (21, 21.0 day)	<0.001*
Aminoglycosides	2 (8.0%) (10–12, 11.0 days)	5 (10.0%) (4–13, 7.6 days)	0.779
Fluoroquinolones	6 (24.0%) (4–13, 7.7 days)	7 (14.0%) (6–17, 11.7 days)	0.281
Metronidazole	4 (16.0%) (4–15, 9.0 days)	9 (18.0%) (4–15, 8.8 days)	0.829
Clindamycin	1 (4.0%) (8, 8.0 day)	2 (4.0%) (6–19, 12.5 days)	1.000
Carbapenems	8 (32.0%) (3–18, 9.6 days)	8 (16.0%) (7–20, 11.9 days)	0.111

(*continued on next page*)

Table 1 (*continued*)

Characteristics	Ertapenem-nonsusceptible group ($n = 25$)	Ertapenem-susceptible group ($n = 50$)	p
	Mean ± SD or No. (%)	Mean ± SD or No. (%)	
Outcome			
Appropriate antibiotic treatment	17 (68.0%)	47 (94.0%)	0.003*
Mortality, ≦14 days	11 (44.0%)	11 (22.0%)	0.049*
Mortality, ≦28 days	13 (52.0%)	15 (30.0%)	0.063
Mortality, overall	15 (60.0%)	20 (40.0%)	0.102
Days from culture to death, overall	11.3 ± 12.7 (0—41)	23.8 ± 31.1 (0—120)	0.117
Favorable (cure or improvement)	9 (36.0%)	30 (60.0%)	0.050
Unfavorable (stationary or deterioration)	16 (64.0%)	20 (40.0%)	

COPD = chronic obstructive pulmonary diseases; H/D = hemodialysis; SD = standard deviation.
* = statistically significant ($p < 0.05$).
[a] Heart diseases included congestive heart failure, ischemic and valvular heart diseases.
[b] Chronic liver diseases included liver cirrhosis and chronic hepatitis.
[c] Immunosuppressant use included administration of steroids or immunosuppressant agents for non-hema-oncologic diseases.
[d] β-lactam-lactamase inhibitors included amoxicillin/clavulanic acid, ampicillin/sulbactam and piperacillin/tazobactam.

accordance with the criteria of the Clinical and Laboratory Standards Institute (CLSI).[21] The antibiotic disks for *Enterobacteriaceae* included amoxicillin-clavulanic acid, piperacillin, piperacillin-tazobactam, cefazolin, cefuroxime, ceftriaxone, ceftazidime, aztreonam, gentamicin, amikacin, ciprofloxacin and ertapenem. Quality control was performed by testing *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, *K pneumoniae* ATCC 700603 and *E coli* ATCC 35218. Interpretations of disk diffusion results were made by using CLSI document M100-S19.[22] The susceptibility of *K pneumoniae* was initially screened with ertapenem disk diffusion testing at the suggestion of CLSI document M100-S19, and was confirmed by imipenem disk diffusion, according to established methods and breakpoints,[22] and by the Etest methods with ertapenem and imipenem, according to the manufacturer's instructions (AB Biodisk, Solna, Sweden).

Definition of appropriateness of antibiotic therapy and outcomes

Appropriate antibiotic therapy was defined as the antibiotics being used for bacteremia were effective *in vitro* against the offending pathogens and had been administered for at least 3 days. The primary outcomes were defined as 14-day mortality, 28-day mortality and overall in-hospital mortality. Secondary outcome was the outcome of the infection and was assessed as either favorable (cure or improvement) or unfavorable (stationary or deterioration).

Statistical methods

Descriptive statistics including mean, standard deviation and range were used to summarize the continuous variables. Descriptive statistics including the number of observations and percentage were used to summarize the categorical variables. For the continuous variables, an independent-*t* test or Mann—Whitney *U* test was considered for the test statistics, depending on the validity of the normality assumption. A Chi-square test or Fisher's exact test was used to test the categorical variables. Multivariate analysis was performed using logistic regression to identify factors that independently and significantly affected outcome. Variables with a p value <0.05 in bivariate analyses were considered for inclusion in a multivariate model. All statistical analyses were performed using standard programs of Statistical Package for the Social Sciences for Windows, version 18.0 (PASW, Chicago, IL, USA).

Results

Study population

From January 2007 to December 2009, there were 1512 patients with *K pneumoniae* bacteremia at our hospital, and 34 of them (2.25%) had ENSKp bacteremia. The prevalence rate increased from 1.72% in 2007 to 2.41% in 2009. By using stepwise matching variables, including gender, age, year of bloodstream pathogen isolation and length of hospital stay up to isolation of *K pneumonia* from blood, 9 ENSKp bacteremia patients were excluded because there were no fully matched

Table 2 Multivariate analysis of risk factors for ertapenem-nonsusceptible *Klebsiella pneumoniae* infection

Factors	Odds ratio	95% Confidence limits	p
Prior exposure to 4th generation Cephalosporins	28.05	(2.92—269.85)	0.004*
Chronic obstructive pulmonary disease	21.38	(2.95—154.92)	0.002*
Pittsburgh bacteremia score	1.35	(1.10—1.66)	0.004*

Only risk factors in Table 1 with p value <0.05 were considered for inclusion in a multivariable analysis.
A multivariable regression model was constructed by using a stepwise selection procedure.
* = statistically significant ($p < 0.05$).

patients with ESKp bacteremia for them. Therefore, 75 patients were included in this study (25 cases with ENSKp bacteremia and 50 controls with ESKp bacteremia). The blood isolates, disc diffusion test and Etest results of the 25 patients with ENSKp bacteremia are shown in Table 3.

Table 3 The analysis of the disc diffusion tests and Etests for 25 ertapenem-nonsusceptible *Klebsiella pneumoniae* blood isolates

No.	Isolates	Disc diffusion test		Etest	
		ETP	IMP	ETP MIC	IMP MIC
1	*K pneumoniae*-ESBL strain	I	S	R = 8	S = 1
2	*K Pneumoniae*	I	S	R = 8	S = 0.25
3	*K pneumoniae*-ESBL strain	R	R	R > 32	R > 32
4	*K Pneumoniae*	I	I	R > 32	R > 32
5	*K pneumoniae*-ESBL strain	R	S	R = 32	S = 4
6	*K pneumoniae*-ESBL strain	R	S	R > 32	S = 1
7	*K Pneumoniae*	R	S	R = 32	S = 0.5
8	*K pneumoniae*-ESBL strain	I	S	R = 16	S = 1
9	*K Pneumoniae*	R	S	R > 32	S = 4
10	*K Pneumoniae*	R	S	R > 32	S = 4
11	*K pneumoniae*-ESBL strain	R	S	R = 8	S = 4
12	*K pneumoniae*-ESBL strain	R	S	R = 32	S = 0.25
13	*K pneumoniae*	I	S	R = 16	S = 4
14	*K pneumoniae*	R	S	R = 8	S = 2
15	*K pneumoniae*-ESBL strain	R	S	R > 32	S = 4
16	*K pneumoniae*-ESBL strain	R	S	R = 16	S = 1
17	*K pneumoniae*	R	S	R > 32	S = 4
18	*K pneumoniae*	I	S	R > 32	I = 8
19	*K pneumoniae*-ESBL strain	I	S	R = 8	S = 1
20	*K pneumoniae*-ESBL strain	I	S	I = 4	S = 0.5
21	*K pneumoniae*-ESBL strain	R	S	R > 32	S = 1
22	*K pneumoniae*-MDR strain	R	R	R > 32	R > 32
23	*K pneumoniae*-ESBL strain	R	S	R > 32	I = 8
24	*K pneumoniae*-MDR strain	R	I	R > 32	R > 32
25	*K pneumoniae*-ESBL strain	R	S	R > 32	S = 2

E ESBL = extended-spectrum-β-lactamase; ETP: ertapenem; IMP: imipenem; I: intermediately resistant; MDR = multidrug resistant; MIC: minimum inhibitory concentration; R: resistant; S: susceptible.
K pneumoniae: 9 isolates; *K pneumoniae*-ESBL strain: 14 isolates, *K pneumoniae*-MDR strain: 2 isolates.
2009 Clinical and Laboratory Standards Institute criteria for MIC: ETP: S: ≦2, I = 4, R: ≧8; IPM: S: ≦4, I = 8, R: ≧16.

Source of bacteremia

The sources of bacteremia were determined by the medical records, image studies, surgical findings and microbiology evidence. The definite source was defined as a culture-proven infection site with the same organism as the blood culture isolate. The possible infection source was defined as a bacteremia plus a clinically suspected infection site without culture proof. In the ENSKp bacteremia group, pneumonia was the most common source (10 patients, 7 definite and 3 possible), and the other sources were as follows: urinary tract infection (4, all definite), catheter-related infection (4, 1 definite and 3 possible), liver abscess with peritonitis (1, definite) and unidentified source (6).

Risk factors

In Table 1, we present the results of the bivariate analysis of matched data regarding risk factors associated with ENSKp bacteremia. Compared with the ESKp group, the ENSKp bacteremia was more frequently seen in patients with a history of chronic obstructive pulmonary disease (COPD) ($p = 0.001$), acute renal failure ($p = 0.021$), chronic kidney disease without dialysis ($p = 0.021$), recent access to health care facilities (i.e., nursing home or hospital) ($p = 0.016$), ICU stay ($p = 0.002$), mechanical ventilation ($p = 0.003$), the placement of central venous catheters ($p = 0.016$), Foley indwelling ($p = 0.022$), simultaneous polymicrobial bacteremia with *K. pneumoniae* isolated from blood ($p = 0.003$), prior exposure to β-Lactam/β-Lactam-lactamase inhibitors ($p = 0.008$) and 4th generation cephalosporins ($p < 0.001$). Surgery during hospitalization was more often seen in patients with ESKp bacteremia (8.0% vs. 32.0%, $p = 0.022$). In addition, a higher disease severity, as indicated by a Pittsburgh bacteremia score, was also observed in patients with ENSKp bacteremia (6.00 ± 3.39 vs. 2.98 ± 2.81, $p < 0.001$).

We applied multivariate analysis to variables that were statistically significant in bivariate analysis. Using a logistic regression model, the multivariate analysis showed that prior exposure to 4th generation cephalosporins (odds ratio [OR], 28.05; 95% confidence interval [CI], 2.92—269.85; $p = 0.004$), history of COPD (OR, 21.38; 95% CI, 2.95—154.92; $p = 0.002$) and higher Pittsburgh bacteremia score (OR, 1.35; 95% CI, 1.10-—.66; $p = 0.004$) were independent factors for the development of ENSKp bacteremia (Table 2).

Outcomes

Compared with the control group, patients with ENSKp bacteremia had a higher overall mortality rate (15/25, 60.0% vs. 20/50, 40.0%, $p = 0.102$). Furthermore, the case group had a higher rate of 14-day mortality than the control groups (11/25, 44.0% vs. 11/50, 22.0%; $p = 0.049$) (Table 1). Unfavorable outcomes were more frequently found in the ENSKp group (64.0% vs. 40.0%), even though there were borderline statistically significant differences ($p = 0.050$).

Seventeen patients with ENSKp bacteremia received appropriate antibiotic treatment, whereas eight received inappropriate antibiotic treatment. Eleven of the 17 patients with ENSKp bacteremia (64.7%) who received appropriate antibiotic treatment died, whereas four of the eight patients (50.0%) who received inappropriate antibiotics died ($p = 0.484$).

Discussion

The emergence of CRKp in recent years and its various resistance mechanisms[5,6,13] have caused global concern because of the threat of the spread of CRKp and limited antibiotics choices. Many studies[12,15–18] investigated the risk factors for CRKp infection but conducted different control groups and few focused on bacteremia, which was a great challenge for physicians.

Our study showed that prior exposure to 4th generation cephalosporins was an independent factor for ENSKp bacteremia and the mean days of its usage were 9.3 days in the case group (4～27 days) (Table 1). Two earlier studies reported that prior exposure to cephalosporins and carbapenems were associated with CRKp infections.[15,17] However, cephalosporins had not been further subdivided for analysis. In another study,[19] prior extended-spectrum cephalosporin use was reported as an independent risk factor but the authors did not mention the association of 3rd or 4th generation cephalosporins. Prior exposure to fluoroquinolones, antipseudomonal penicillins or carbapenems was reported as independent risk factor of CRKp infections by several investigators[12,16,18] but this was not seen in our study.

COPD was another independent factor for ENSKp bacteremia in our study. A matched case-control study by Falagas et al, which focused not only on bacteremia but also on other sites of infection, reported that COPD was associated with CRKp infections in bivariate analysis.[16] Frequent pulmonary infections, repeated hospitalization and multiple courses of antibiotic use were common in patients with COPD.[23] As we look to the COPD patients in our study, pneumonia as the source of bacteremia was noted in four of eight patients in the case group but not in the two patients in the matched controls.

Bivariate analysis in this study revealed that polymicrobial bacteremia was more frequently seen in the case group than in the controls (36.0% vs. 8.0%). The concurrent blood isolates in the case group included methicillin-resistant *Staphylococcus aureus*, ESBL-producing *E coli*, *Pseudomonas aeruginosa*, *Pseudomonas cepacia*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, and glucose-nonfermenting Gram-negative bacilli, which mostly were nosocomial pathogens.

The strikingly crude and attributable mortality rates associated with CRKp bacteremia have been reported before[24] but the control was defined as patients who were very similar to case subjects except that they did not have bacteremia. In this study the case group had a statistically significant higher rate of 14-day mortality than the controls. This might be attributed to ENSKp bacteremia and a lower percentage of appropriate antibiotic treatment in the case group (68.0% vs. 94.0%). Both of the 28-day mortality and overall in-hospital mortality rates were higher in the case group but there were no statistically significant difference between both groups ($p = 0.063$ and $p = 0.102$, respectively), which may be partially influenced by other factors such as disease severity or underlying diseases.

There were several limitations to our study. First, the number of patients included in our study is relatively small, although ertapenem resistance in *K pneumoniae* is rare.[25] Second, we focused on bacteremia and only included 73.5% (25/34) ENSKp bacteremia patients, who had fully matched controls using stepwise matching variables. Furthermore, molecular epidemiology investigation for ertapenem-resistant mechanisms among these *K pneumoniae* blood isolates was not performed although different resistant mechanisms may influence treatment outcomes.[16]

In conclusion, this study provided our experience for risk factors of the acquisition of ENSKp bacteremia and the associated clinical outcomes. ENSKp bacteremia had a higher 14-day mortality rate and a poor outcome, and was associated with prior exposure to 4th generation cephalosporins, COPD and higher Pittsburgh bacteremia score. Antibiotic stewardship may be the solution for a preventive strategy.

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