Clinical Impact and Risk Factors of Nonsusceptibility to Third-Generation Cephalosporins Among Hospitalized Adults With Monomicrobial *Enterobacteriaceae* Bacteremia in Southern Taiwan: A Multicenter Study

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Research

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Abstract

Background: Reducing effectiveness of broad-spectrum cephalosporins against *Enterobacteriaceae* infections has been recognized. This study aimed to investigate risk factors and clinical significance of third-generation cephalosporin nonsusceptibility (3GC-NS) among the cases of monomicrobial *Enterobacteriaceae* bacteremia (mEB) at regional or district hospitals.

Methods: The study was conducted at three hospitals at southern Taiwan between Jan. 2017 and Oct. 2019. Only the first episode of mEB from each adult (aged ≥20 years) was included. The primary outcome was in-hospital crude mortality.

Results: Overall there were 499 episodes of adults with mEB included, and their mean age was 74.5 years. Female predominated, accounting for 53% of all patients. *Escherichia coli* (62%) and *Klebsiella pneumoniae* (21%) were two major causative species. The overall mortality rate was 15% (73/499), and patients infected by 3GC-NS isolates (34%, 172/499) had a higher mortality rate than those by 3GC-susceptible isolates (66%, 327/499) (21% *vs.* 11%, *P*=0.005). By the multivariate analysis, 3GC-NS was the only independent prognostic determinant (adjusted odds ratio [AOR], 1.78; *P*=0.04). Of note, male (AOR 2.02, *P*=0.001), nosocomial-acquired bacteremia (AOR 2.77, *P*<0.001), and usage of nasogastric tube (AOR 2.01, *P*=0.002) were positively associated with 3GC-NS, but *P. mirabilis* bacteremia (AOR 0.28, *P*=0.01) and age (AOR 0.98, *P*=0.04) negatively with 3GC-NS.

Conclusion: For adults with *Enterobacteriaceae* bacteremia, 3GC-NS signifies a significant prognostic impact. Efforts to rapid identification of such antimicrobial resistance profiles should be incorporated into antimicrobial stewardship programs to achieve favorable outcomes.

Background

Enterobacteriaceae isolates are responsible for a wide variety of nosocomial and community-acquired infections and third-generation cephalosporins (3GCs) are administered as the main choice for the treatment of infections caused by these microorganisms [1–7]. However, along with the over-prescription of 3GCs by clinicians, reducing therapeutic efficacy of these antimicrobial agents for *Enterobacteriaceae* infections [1, 7–11] and the increasing trend in non-susceptibility (NS) to 3GCs were recently evidenced [12]. Moreover, infections caused by 3GC-resistant *Enterobacteriaceae* were significantly associated with the increasing hazard of death and excess length of stay and costs [13]. Taking *Escherichia coli* as an example, the total cost attributable to excess hospital stays for bloodstream infections caused by 3GC-resistant isolates was estimated up to 18.1 million Euros each year in Europe [14]. Furthermore, for patients with *Enterobacter* bacteremia, the 30-day mortality rate of patients infected by 3GC-resistant isolates was significantly higher than those by 3GC-susceptible isolates, regardless of whether stratified by infection sites or by the initial presence of septic shock [15].

In a medical center in northern Taiwan, the overall proportion of 3GC resistance in community-onset *E. coli* bacteremia has been up to 19.7% [16]. Nevertheless, clinical impact of 3GC resistance on the

prognoses of patients with *Enterobacteriaceae* bacteremia in district or regional hospitals in Taiwan was not reported yet. Accordingly, the aim of the present multicenter study was to investigate risk factors of 3GC-NS *Enterobacteriaceae* bacteremia and their adverse influence on outcomes.

Methods

Study design and population

The study was conducted at three hospitals of Ministry of Health and Welfare in southern Taiwan: Tainan Hospital (A, a 300-bed district hospital), Sinying Hospital (B, a 78-bed regional hospital), and Chiayi Hospital (C, a 237-bed regional hospital). There were infection-disease specialists dealing with antibiotic stewardship program at the study hospitals. The study periods spanned between Jan. 1, 2017 and Oct. 31, 2019. The episodes of monomicrobial *Enterobacteriaceae* bacteremia (mEB) in hospitalized adults (aged ≥ 20 years) were analyzed, and only the first episode in each patient was included during the study period. The study was reviewed and approved by the Institutional Review Board of National Cheng Kung University Hospital (A-ER-105-183).

Data collection

By reviewing the electronic medical charts, a predetermined form was adapted to collect clinical characters, in terms of patient gender, age, hospitalization duration, usage of vasopressor agents and antimicrobials, types and severity (Charlson comorbidity index) of comorbidities, laboratory data, and clinical outcomes. The primary outcome was the in-hospital crude mortality after bacteremia onset. Patients were excluded if they had incomplete clinical information.

Microbiological methods

Blood cultures were processed in the BD BACTEC 9240 system (Becton Dickinson, USA). Bacterial species were identified by the morphology and color in the chromogenic agar, and confirmed by BD GNB ID or BD E/NF crystal kit (Becton Dickinson, USA). Antibiotic susceptibility was determined by the disk diffusion method, in accordance with the procedures of the Clinical and Laboratory Standards Institute (CLSI), and was interpreted according to the zone criteria of CLSI issued in 2018 (M100-S21) [17]. The drugs tested included ampicillin, ampicillin/sulbactam, gentamicin, amikacin, cefazolin, cefuroxime, ceftriaxone, ceftazidime, cefepime, ciprofloxacin, ertapenem, and imipenem or meropenem. Susceptibility to 3GCs was defined as the clear zone diameter of ceftriaxone $\geq$ 23 mm, cefotaxime $\geq$ 26 mm, or ceftazidime $\geq$ 21 mm [17], and susceptibility to fluoroquinolones as the clear zone diameter of levofloxacin $\geq$ 17 mm or ciprofloxacin $\geq$ 21 mm [17].

Definitions

Bacteremia was defined as bacterial growth of blood cultures drawn from central or peripheral venipuncture. As previously described [18, 19], the administration of antimicrobial therapy was considered to be appropriate when all the following criteria were fulfilled: (i) the administrated antimicrobial was *in*

vitro active against causative microorganisms isolated from blood cultures, based on the contemporary CLSI breakpoints [17]. (ii) the route and dosage of antimicrobials were administered as recommended in accordance with the Sanford Guide to Antimicrobial Therapy 2018 [20]. As the previous definition [21], antimicrobials administered within three days after bacteremia onset were regarded as empirical therapy, and those administered after three days of onset when the identification and susceptibility data of bacteremic isolates were available were referred as definitive therapy. Nosocomial bacteremia was defined the onset of bacteremia occurring at ≥48 hours after admission [22].

Septic shock was defined as a mean arterial pressure of < 75 mmHg and usage of vasopressor administration [23]. Comorbidities were defined as described previously [24]. Malignancies included hematological malignancies and solid tumors. The severity of preexisting medical diseases was assessed by a previously delineated classification system (Charlson comorbidity index) [25]. Crude mortality was defined as the death from all causes.

Statistical analysis

Statistical analysis was performed by the statistical software (SPSS, version 13.0). Descriptive statistics, including the means, standard deviations, and ranges, were used to analyze the continuous variables. For categorical variables, the percentages and confidence intervals were used. The independent-t test was applied for the continuous variables and the chi-square test or Fisher's exact test for the categorical variables. To identify the predictors and impact of 3GC NS, the variables with a *P* value less than 0.1 recognized by the univariate analysis were processed by a stepwise, backward logistic regression model. A two-tailed *P* value of less than 0.05 was considered to be statistically significant.

Results

Patient demographics

After excluding recurrent episodes and polymicrobial bacteremia, there were 293, 88, and 118 episodes of mEB in the hospital A, B and C, respectively, were included for the analysis (Fig. 1). The crude in-hospital mortality rate was similar in three hospitals: 15%, 16%, and 13%, respectively. Overall, this study involved 499 adults with an average age of 75 years and their crude in-hospital mortality rate was 15%. Female gender (263, 53%) predominated. Common comorbidities of the included patients included hypertension, diabetes mellitus, old stroke, chronic kidney diseases, and malignancy, and in this study major microorganisms causing mEB were *E. coli, Klebsiella pneumoniae, Proteus mirabilis, Providencia stuartii*, and *Citrobacter koseri* (Table 1).

Table 1
Factors associated with in-hospital crude mortality in patients with monomicrobial *Enterobacteriaceae* bacteremia.

Variables	Total	Patient numbers (%)		*P* value
	n = 499	Survived, n = 426	Expired, n = 73	
Age, years, mean ± SD	74.5 ± 12.9	74.1 ± 13.0	77.3 ± 11.5	0.05
Gender, male	236 (47.3)	201 (47.2)	35 (47.9)	1.00
Comorbidities				
Hypertension	286 (57.3)	246 (57.7)	40 (54.8)	0.70
Diabetes mellitus	207 (41.5)	177 (41.5)	30 (41.1)	1.00
Old stroke	105 (21.0)	86 (20.2)	19 (26.0)	0.28
Chronic kidney diseases	79 (15.8)	64 (15.0)	15 (20.5)	0.23
Malignancy	66 (13.2)	54 (12.7)	12 (16.4)	0.36
Coronary artery disease history	58 (11.6)	48 (11.3)	10 (13.7)	0.55
Liver cirrhosis	22 (4.4)	18 (4.2)	4 (5.5)	0.55
Congestive heart failure	14 (2.8)	13 (3.1)	1 (1.4)	0.70
Charlson comorbidity index, mean ± SD	1.2 ± 1.2	1.2 ± 1.1	1.4 ± 1.3	0.15
Nosocomial bacteremia	112 (22.4)	91 (21.4)	21 (28.8)	0.17
Time-to-positivity, hours	25.1 ± 17.4	24.5 ± 17.4	28.5 ± 19.4	0.10
Antimicrobial-susceptible isolates				
Second GCs	223 (44.7)	197 (46.2)	26 (35.6)	0.10
Third GCs	**327 (65.5)**	**290 (68.1)**	**37 (50.7)**	**0.005**
Fourth GCs	363 (72.7)	316 (74.2)	47 (64.4)	0.09
Amoxicillin/clavulanic acid	297 (57.5)	250 (58.7)	37 (50.7)	0.20
Fluoroquinolones	259 (51.9)	224 (52.6)	35 (47.9)	0.53
Ertapenem	**465 (93.2)**	**403 (94.6)**	**62 (84.9)**	**0.009**

GC = generation cephalosporin; SD = standard deviation.

Data are given as number (percent), unless otherwise specified.

Boldface indicates statistical significance in the univariate analysis, *i.e.*, a *P* value of < 0.05.

Variables	Total	Patient numbers (%)		*P* value
	n = 499	Survived, n = 426	Expired, n = 73	
Major causative microorganisms				
Escherichia coli	**310 (62.1)**	**275 (64.6)**	**35 (47.9)**	**0.009**
Klebsiella pneumoniae	**104 (20.8)**	**80 (18.8)**	**24 (32.9)**	**0.008**
Proteus mirabilis	31 (6.2)	27 (6.3)	4 (5.5)	1.00
Providencia stuartii	11 (2.2)	10 (2.3)	1 (1.4)	1.00
Citrobacter koseri	8 (1.6)	7 (1.6)	1 (1.4)	1.00
GC = generation cephalosporin; SD = standard deviation.				
Data are given as number (percent), unless otherwise specified.				
Boldface indicates statistical significance in the univariate analysis, *i.e.*, a *P* value of < 0.05.				

Risk Factors Of In-hospital Crude Mortality

As compared with the survivors, fatal patients with mEB were less likely to be infected by 3GC- (68% *vs.* 51%, *P* = 0.005) or ertapenem-susceptible isolates (95% *vs.* 85%, *P* = 0.009) and *E. coli* (65% *vs.* 48%, *P* = 0.008) (Table 1), but were often associated with *K. pneumoniae* infections (19% *vs.* 33%, *P* = 0.008). No significant association between the in-hospital mortality and patient age, gender male, comorbidity types or Charlson comorbidity index was disclosed. Notably, in the multivariate analysis for risk factors of in-hospital crude mortality, only one independent variable, 3GC-NS, was recognized (adjusted odds ratio [AOR], 1.78; 95% confident interval [CI] 1.02–3.11; *P* = 0.04) (Table 2).

Table 2
Multivariate analysis of risk factors for in-hospital crude mortality among adults with monomicrobial *Enterobacteriaceae* bacteremia.

Characters	Adjusted odds ratio	95% confidence interval	*P* value
3GC non-susceptibility	**1.78**	**1.02–3.11**	**0.04**
Ertapenem non-susceptibility	1.55	0.61–3.91	0.36
Klebsiella pneumoniae	1.12	0.51–2.49	0.78
Escherichia coli	0.60	0.31–1.19	0.14
3GC = third-generation cephalosporin.			

Predictors of 3GC-non-susceptibility among Enterobacteriaceae **bacteremia**

Patients infected by 3GC-NS isolates were older (mean age: 77 years vs. 74 years; P = 0.009) and more likely to be male gender (58% *vs.* 42%, *P* < 0.001), or to have comorbidities of chronic kidney diseases (23% *vs.* 12%, *P* = 0.003) or the use of nasogastric tubes (61% *vs.* 37%, *P* < 0.001) or urinary catheters (55% *vs.* 38%, *P* < 0.001) than those by 3GC-susceptible microorganisms, as shown in Table 3. Otherwise, less episodes of *P. mirabilis* bacteremia (3% *vs.* 8%, *P* = 0.03) and more *K. pneumoniae* bacteremia (30% *vs.* 16%, *P* < 0.001) were noted in patients with 3GC-NS *Enterobacteriaceae* bacteremia (Table 3). Since chronic kidney disease was the only parameter in Charlson comorbidity index with statistically correlated with 3GC-NS, chronic kidney disease, instead of Charlson comorbidity index, was placed in the multivariate analysis. In the multivariate analysis, male patients (AOR 2.02, 95% CI 1.33–3.05; *P* = 0.001), nosocomial-acquired bacteremia (AOR 2.77, 95% CI 1.72–4.47; *P* < 0.001), and usage of nasogastric tube (AOR 2.01, 95% CI 1.28–3.16; *P* = 0.002) were positively associated with 3GC-NS (Table 4). In contrast, *P. mirabilis* bacteremic episodes (AOR 0.28, 95% CI 0.10–0.77; *P* = 0.01) and age (AOR 0.98, 95% CI 0.97–0.99; *P* = 0.04) were negatively linked to 3GC-NS.

Table 3
Clinical predictors of third-generation cephalosporin-non-susceptibility in the episodes of monomicrobial *Enterobacteriaceae* bacteremia.

Variables	**Patient numbers (%)**		***P* value**
	Susceptible, n = 327	**Non-susceptible, n = 172**	
Age, years, mean ± SD	**73.5 ± 13.0**	**76.6 ± 12.3**	**0.009**
Charlson comorbidity index, mean ± SD	**1.1 ± 1.1**	**1.4 ± 1.2**	**0.007**
Gender, male	**137 (41.9)**	**99 (57.6)**	**< 0.001**
Comorbidities			
Hypertension	190 (58.1)	96 (55.8)	0.64
Diabetes mellitus	133 (40.7)	74 (43.0)	0.63
Old stroke	68 (20.8)	37 (21.5)	0.91
Chronic kidney disease	**40 (12.2)**	**39 (22.7)**	**0.003**
Malignancy	43 (13.1)	23 (13.4)	1.00
Coronary artery disease	32 (9.8)	26 (15.1)	0.08
Liver cirrhosis	12 (3.7)	10 (5.8)	0.26
Congestive heart failure	8 (2.4)	6 (3.5)	0.57
Nosocomial bacteremia	**48 (14.7)**	**64 (37.2)**	**< 0.001**
Catheter dependence			
Nasogastric tube	**120 (36.9)**	**104 (60.8)**	**< 0.001**
Urinary catheter	**124 (37.9)**	**94 (55.3)**	**< 0.001**
Major causative microorganisms			
Escherichia coli	210 (64.2)	100 (58.1)	0.21
Klebsiella pneumoniae	**51 (15.6)**	**52 (30.2)**	**< 0.001**
Proteus mirabilis	**26 (7.9)**	**5 (2.9)**	**0.03**
Providencia stuartii	10 (3.1)	1 (0.6)	0.11
Citrobacter koseri	6 (1.8)	2 (1.2)	0.72

SD = standard deviation.

* Data are given as number (percent), unless otherwise specified. Boldface indicates statistical significance in the univariate analysis, *i.e.*, a *P* value of < 0.05.

Table 4
Multivariate analysis of risk factors of third-generation cephalosporin non-susceptibility among the episodes of monomicrobial *Enterobacteriaceae* bacteremia.

Characters	Adjusted odds ratio	95% confidence interval	*P* value
Patient demographics			
Male	**2.02**	**1.33–3.05**	**0.001**
Age, years	**0.98**	**0.97–0.99**	**0.04**
Nosocomial bacteremia	**2.77**	**1.72–4.47**	**< 0.001**
Catheter dependence			
Nasogastric tubes	**2.01**	**1.28–3.16**	**0.002**
Urinary catheters	1.39	0.89–2.18	0.15
Causative microorganisms			
Klebsiella pneumoniae	1.48	0.90–2.45	0.13
Proteus mirabilis	**0.28**	**0.10–0.77**	**0.01**
Underlying chronic kidney diseases	1.58	0.93–2.69	0.09

Antimicrobial Therapy And Clinical Outcomes

The common antimicrobials empirically administered for patients with 3GC-susceptible *Enterobacteriaceae* bacteremia were 3GCs (32%), 2GCs (16%), and piperacillin-tazobactam (14%). Appropriate empirical (30% *vs.* 82%, *P* < 0.001) or definitive (80% *vs.* 94%, *P* < 0.001) therapy was less commonly prescribed among patients infected by 3GC-NS isolates, compared to those by 3GC-susceptible isolates (Table 5). Furthermore, patients with 3GC-NS *Enterobacteriaceae* bacteremia more often had septic shock at presentation (20% *vs.* 11%, *P* = 0.007) and had a higher in-hospital crude mortality rate (21% *vs.* 11%, *P* = 0.005) than those infected by 3GC-susceptible isolates (Table 5).

Table 5. Bacteremia severity, antimicrobial therapy and outcomes of patients with monomicrobial *Enterobacteriaceae* bacteremia, stratified by third-generation cephalosporin susceptibility.

Variables	Patient numbers (%)		*P* value
	Susceptible, n=327	Non-susceptible, n=172	
Bacteremia severity			
Blood leukocyte, x10^3/mm^3, mean ± SD	13.3 ± 7.4	13.0 ± 6.0	0.72
Time-to-positivity, hours, mean ± SD (n=392)	24.5 ± 16.6	26.1 ± 19.5	0.39
Initial presentation of septic shock	36 (11.0)	35 (20.3)	0.007
Requirement of intensive care	61 (18.7)	33 (19.2)	0.90
Appropriate antimicrobial therapy			
Empirical	267 (81.7)	52 (30.2)	<0.001

Definitive	**307 (93.9)**	**138 (80.2)**	**<0.001**
Outcomes			
Length of hospitalization, days, mean ± SD	**20.2 ± 58.1**	**26.9 ± 41.3**	**0.15**
In-hospital crude mortality	**37 (11.3)**	**36 (20.9)**	**0.005**

SD = standard deviation.

*** Data are given as number (percent), unless otherwise specified. Boldface indicates statistical significance under the univariate analysis, *i.e.,* a *P* value of <0.05.**

Discussion

Patients with 3GC-NS mEB were associated with longer hospital or ICU stays and a worse outcome. However, such a result needs to be interpreted with caution, because patients infected by the isolates of antimicrobial-resistant *Enterobacteriaceae* were older and had more comorbidities [1, 26]. Moreover, the other explanation for unfavorable prognoses might result from delayed administration of appropriate antibiotics [18, 19]. Similar to the previous report [1], inadequate empirical antibiotic therapy was more commonly in patients with 3GC-NS mEB than those with bacteremia due to 3GC-susceptible *Enterobacteriaceae* isolates.

In our study, male patients, nosocomial-acquired bacteremia, and usage of nasogastric tube were positively associated with 3GC-NS; and in contrast, *P. mirabilis* bacteremic episodes and age were negatively linked to 3GC-NS. Factors correlating to the acquisition of *Enterobacteriaceae* strains harboring 3GC resistance have been identified before, including male gender [1], prior exposure to antimicrobial agents [1, 16, 26], underlying disease[1, 16, 26], indwelling device or prosthesis[16, 26], or surgery [26]. Likewise, several variables, including male gender, age, usage of nasogastric tube, and bacteremic episodes due to *K. pneumoniae*, were independently linked to 3GC-NS mEB in our cohort. However, some predictors identified in previous investigations[1, 16, 26], such as the presence of an invasive prosthesis or

intravascular catheter, recent surgery or hospitalization, or residence in nursing-home or long-term care facility were not assessed in the present retrospective study.

The ratio of appropriate empirical therapy was lower among patients infected by either 3GC-NS (30%) or 3GC-susceptible isolates (82%) in our study. In a retrospective Dutch study of bacteremia episodes caused by 3GC-resistant and 3GC-sensitive *Enterobacteriaceae* bacteremia in 2015, 56% and 94% were empirically treated with appropriate antibiotics, respectively [27]. Nevertheless the 3GC-resistant rate in the former study was 8.3% (64/773) [27], much lower than the 3GC-NS rate of 34.5% (172/499) in our study. The higher non-susceptible rates toward antimicrobial agents among *Enterobacteriaceae* bacteremia isolates in recent years led clinicians more difficult in selecting appropriate empirical antimicrobial agents, especially for extended-spectrum β-lactamase (ESBL)-producing bacteria [28]. Though ESBL-producing phenotype was not examined, the high 3GC-NS rate among our *Enterobacteriaceae* isolates might partly be contributed by the presence of ESBL-producing isolates. In the era of reduced susceptibility to 3GCs among *Enterobacteriaceae* isolates, the information of the clinical parameters predictive of 3GC-NS identified in our study is helpful to select appropriate antimicrobial agents.

There were several limitations in this study. First, though there were only nearly 500 cases of mEB included in the cohort, it is a multicenter study conducted at three district and regional hospitals in southern Taiwan, representing the population other than the patients cared at medical centers. Second, recall biases due to the retrospective nature of study design unavoidably exist, and the number of factors related to 3GC NS are likely to be underestimated. Third, not all 3GCs (such as cefotaxime, ceftriaxone, and ceftazidime) were tested for the antimicrobial susceptibility. Overestimating or underestimating 3GC-NS among the included *Enterobacteriaceae* isolates is not known, and the study results should be interpreted cautiously. Last, other clinical variables, such as the degree or timing of source control, or the dosage or regimens of antimicrobial therapy were assessed as the potential ones affecting the prognosis of the cases of mEB.

Conclusion

In conclusion, the presence of 3GC-NS in the etiological pathogens of mEB is independently correlated with a poor prognosis. Rapid identification of antimicrobial resistance by clinical predictors or new methods of susceptibility testing shall be incorporated in antimicrobial stewardship programs to improve patient outcomes.

Abbreviations

AOR: adjusted odds ratio; CI: Confidence interval; CLSI: Clinical and Laboratory Standards Institute; *E. coli*: *Escherichia coli*; ESBL: extended-spectrum β-lactamase

GC: generation cephalosporin; 3GC: third-generation cephalosporin; mEB: monomicrobial *Enterobacteriaceae* bacteremia; NS: nonsusceptibility;OR: Odds ratio

SD: standard deviation

Declarations

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Authors' contributions

T.C.L, Y.P.H, and W.C.K. conceived the project and wrote the manuscript. T.C.L, Y.P.H, W.C.K, and Y.L.H. designed the experiments and manuscript revisions. W.T.L, L.C.H, W.D, and C.S.K. collected the clinical data and performed experiments. T.C.L, Y.P.H, and W.C.K. conducted statistical analysis. All authors reviewed the manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

All the data of this article is available from the corresponding author if reasonably requested.

Ethics approval and consent to participate

The study was reviewed and approved the Institutional Review Board of National Cheng Kung University Hospital (A-ER-105-183). Informed consent was waived because of the retrospective nature of the study and the analysis used anonymous clinical data.

Consent for publication

Not applicable.

Competing interests

All authors declare that they have no competing interests.

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Figures

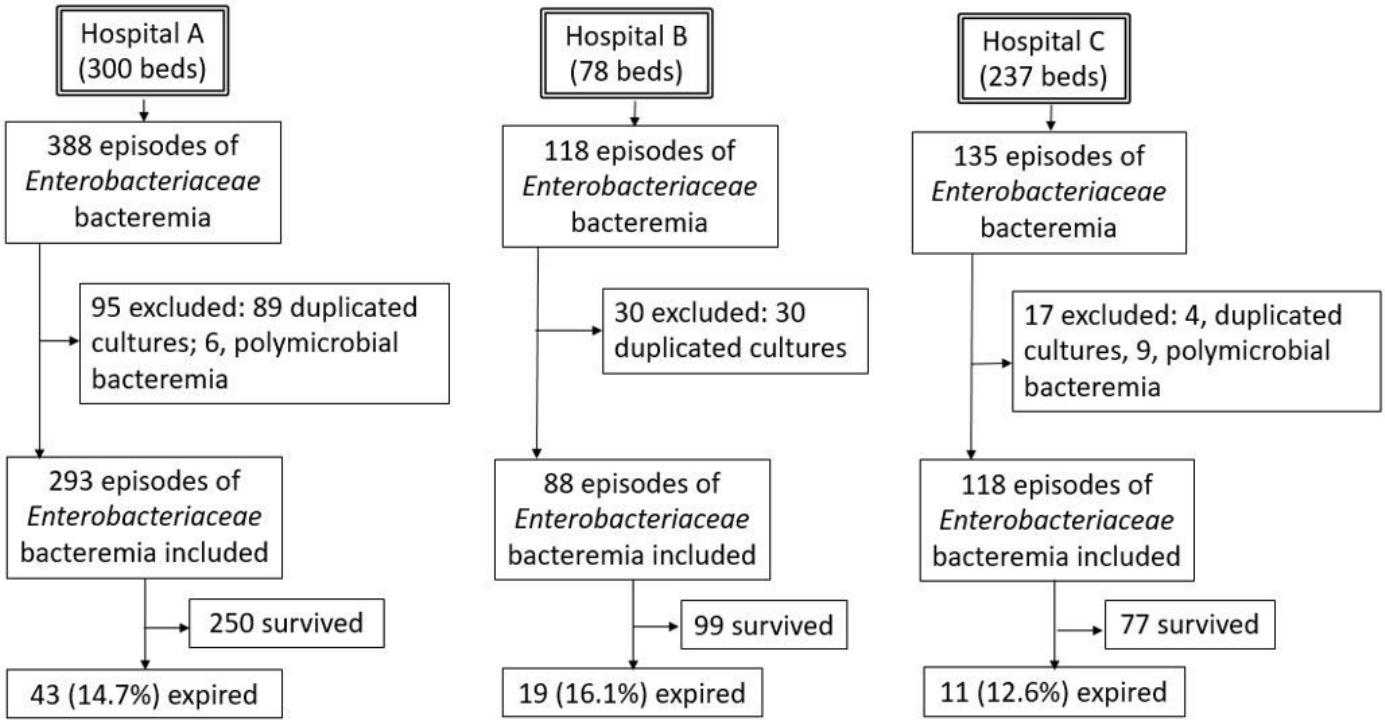

Figure 1

A flowchart of patient selection in three study hospitals.