Incidence and risk factors for acquired colonization and infection due to extended-spectrum beta-lactamase-producing Gram-negative bacilli a retrospective analysis in three ICUs with low multidrug resistance rate

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Incidence and risk factors for acquired colonization and infection due to extended spectrum beta-lactamase-producing Gram-negative bacilli: a retrospective analysis in three ICUs with low multidrug resistance rate.

Running title: Risk factor of ESBL-GNB colonization and infection.

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ABSTRACT

Purpose:

To assess risk factors for the acquisition of extended-spectrum β-lactamase-producing Gram-negative bacilli (ESBL-GNB) colonization and infection (AI) in ICUs with low ESBL-GNB prevalence rate.

Methods:

We conducted a retrospective observational study in three ICUs in Bretagne, France. All patients admitted from January 2016 to September 2017 with a length of stay of two days or more were included. Universal screening for ESBL-GNB colonization was performed in all participating ICUs.

Results:

Of the 3250 included patients, 131 (4.0%) were colonized at admission, 59 acquired colonization while hospitalized (1.9%; 95% CI [1.5%–2.5%]) and 15 (0.5%; 95% CI [0.3%–0.8%]) acquired ESBL-GNB infections. In case of infection, the specificity and the negative predictive values of preexistent colonization for the ESBL-GNB etiology were 93.2% [91.5%–95.1%] and 95.2% [93.5%–97.1%], respectively. Colonization was the main risk factor for ESBL-GNB AI (OR=9.61; 95% CI [2.86–32.29]; $p < 0.001$). Antimicrobial susceptibility of non-ESBL GNB isolates responsible for AI was similar for any non-carbapenem β-lactam (95%) and imipenem (94%).

Conclusion:

ESBL-GNB AIs were rare in ICUs with low ESBL-GNB prevalence rate. Prior colonization was the main risk factor for subsequent infection. Empirical carbapenem therapy could be avoided in non ESBL-GNB colonized patients with suspected AI.

Keyword:

Extended-spectrum beta-lactamase-producing *Enterobacteriaceae*, Gram-negative bacteria, Decontamination, Healthcare-Associated Pneumonia, Bacteremia.

INTRODUCTION

Critically ill patients in the intensive care unit (ICU) have a high risk of acquired infections (AIs) (1,2), which increase morbidity and, to some extent, mortality (3). Pneumonia and bloodstream infection (BSI) are the most common infections with a reported incidence rate of 15 per 1,000 ventilator-days (2) and 9.5 per 1,000 patient-days (1), respectively. Among multidrug-resistant organisms (MDROs) (4-7), extended-spectrum beta-lactamase-producing Gram-negative bacilli (ESBL-GNB) have an increasing prevalence reaching critical point in some ICUs (7,8), leading to the unrestricted use of carbapenems in order to avoid inappropriate antimicrobial therapy (8,9,10).

The challenge of ESBL-GNB has been overemphasized (11) as compared with real life in specific locations. In contrast, risk factors for ESBL-GNB acquired colonization and infection have been unfrequently assessed in ICUs with lower prevalence rates (12-15). The identification of risk factors could help clinicians to target the use of broad-spectrum antibiotics in this setting. The aim of our study was to assess the incidence and risk factors for ESBL-GNB acquired colonization and infection in ICUs with low prevalence of ESBL-GNB.

MATERIALS AND METHODS

Settings and patients

We conducted a retrospective observational study in three French ICUs. The largest ICU (ICU 1) was a medical unit with 22 acute-care beds in a tertiary care university hospital. Unlike the two other centers, this ICU used multiple-site decontamination in intubated patients. It consists of the administration of topical antibiotics (tobramycin, colistin and amphotericin B) four times daily in the oro-pharynx and the gastric tube, chlorhexidine body washing and nasal mupirocin, in all intubated patients for the period of intubation (16). The other two units were polyvalent ICUs with 14 beds (ICU 2) and 12 beds (ICU3). Every ICU followed the recommendations of the French Society for Hospital Hygiene regarding the prevention and treatment of AI (available at https://sf2h.net). Each center had a nosocomial infection committee for the prevention and prospective census of AI.

We screened all admitted patients from January 1st 2016 to September 10th 2017. Patients with a length of stay of two days or more were included. Because rectal screening for ESBL-GNB colonization and report of AIs are routine care, the institutional ethics committee approved the study and the requirement for written informed consent was waived.

Data collection and definitions

ESBL-GNB carriage was screened on a rectal swab at admission, every week afterwards and at ICU discharge. Samples were then inoculated onto antibiotic selective agar. The synergy between third generation cephalosporin and clavulanate was confirmed using a double-disk synergy test.

Colonization at admission was defined as a positive first rectal swab for ESBL-GNB performed within 48 hours of admission. Acquisition of colonization was defined as a subsequent positive rectal swab after a negative first swab. Patients with ESBL-GNB AI were considered colonized prior to infection if their screening rectal swab was positive either before or on the day of the microbial diagnosis of infection.

Infection was considered acquired in the ICU when it was diagnosed 48 hours after admission and was not incubating on admission. The diagnosis of pneumonia included both ventilator-associated pneumonia and ICU-acquired pneumonia that developed in non-ventilated patients and was made based on clinical signs (fever), radiological findings (new infiltrate on chest-X-ray or CT scan), and a positive microbiological culture of an endotracheal aspirate ($\geq 10^6$ colony-forming units/mL) or a broncho-alveolar lavage ($\geq 10^4$

colony-forming units/mL). BSI was diagnosed following one or more positive blood culture as defined by the CDC (17).

For the purpose of this study, we estimated the number of days with colonization and the number of days without colonization before the occurrence of ESBL-GNB infection according to the method reported by Frencken et al. (13) (supplementary Figure 1).

Other collected data were age, sex, reason for admission (medical/surgical), simplified acute physiology score II (SAPS II) at admission, length of stay in ICU, intubation for more than two days, admission in ICU 1 versus ICU 2 and 3 and outcome.

Primary and secondary objectives

The primary objective of the study was to assess the incidence and risk factors of ESBL-GNB acquired colonization and infection. Spectrum of AIs and antimicrobial susceptibility were secondary objectives.

Statistical analysis

Statistical analysis was performed with the statistical software R 3.4.3. Incidence rate and prevalence were expressed with the 95 percent confidence interval (95% CI), categorical variables were expressed as number (percentage) and continuous variables as median and interquartile range (IQR). When appropriate, the chi-square test and the Fisher's exact test were used to compare categorical variables. The Man-Whitney U test and the Kruskal-Wallis test were used for continuous variables when applicable. Multivariate logistic regression analysis was used to study risk factors for ESBL-GNB acquired colonization and acquired infection. Variables with a p-value <0.2 in the univariate analysis or those clinically relevant irrespective of the p-value were included for the multivariate analysis. All tests were two-sided, and a P-value less than 0.05 was considered statistically significant.

RESULTS

Study population

Among 3,861 admitted patients, 3,250 with an ICU length stay of two days or more were all included in the study (Figure 1). SAPS II was 40 [28–56] and age was 62.1 years [51.0–71.0]. One hundred and thirty-one patients (4.0%) were colonized with ESBL-GNB at admission, varying from 2.0% to 4.8% depending on the ICU (Table 1, supplementary Table 1). One thousand five hundred and seven patients (46.4%) were intubated for more than 48 hours. The average length of stay in ICU was 4 days [3–9] and overall ICU mortality was 19.8%.

ESBL-GNB acquired colonization

Among the 3,119 patients not colonized at admission, 59 (1.9%; 95% CI [1.5–2.5]) acquired ESBL-GNB colonization during their ICU stay with a median length of stay of 7 days [5–14] before colonization acquisition. These patients had a higher SAPS II score than those without acquired ESBL-GNB colonization (48 [34–62] vs 39 [28–55], p=0.01). Intubation for 48 hours or more (OR = 6.02 [2.86–12.68], p< 0.001) and admission in ICU 1 (OR = 0.39 [0.22–0.70], p=0.002) were independent risk factors for ESBL-GNB acquired colonization (Table 2).

ESBL-GNB acquired infection

Fifteen infections occurred during a total of 25,857 patient-days at risk, with calculated incidence rates of 0.46 per 100 admissions [0.26–0.76] and 0.58 per 1,000 patient-days [0.49–0.68]. Six cases (40%) had prior ESBL-GNB colonization and 9 had not (Table 3), yielding incidence density rates of 4.73 per 1,000 days with colonization and 0.37 per 1,000 days without colonization respectively (incidence rate ratio 12.86 [4.08–39.31]; $p < 0.001$). There were 8 pneumonias (0.3% [0.1%–0.5%]) and 7 BSIs (0.2% [0.1%–0.4%]) (Table 3). The delay to the onset was similar between cases with and cases without prior colonization (p=0.82). Mortality in the ICU was similar between patients with ESBL-GNB AI and those with other AIs (33.3% versus 32.8%, p=0.92).

One hundred and ninety-two patients (5.9%) acquired 204 infections (pneumonia: 122; BSI: 82) not due to ESBL-GNB. Among the 207 patients who acquired any type of infection, 19 had previous ESBL-GNB colonization. In these patients, 6 acquired ESBL-GNB infection (31.6%), whereas 9 over 188 non- colonized patients (4.8%) acquired ESBL-GNB infection (relative risk 6.60 [2.23–17.57]). The positive and negative predictive values of ESBL-GNB colonization for ESBL-GNB etiology of AI were 31.6% [14.5%–50.5%] and 95.2% [93.5%–97.1%], respectively, whereas sensitivity and specificity were 40.0%, [18.4%– 64.0%] and 93.2% [91.5%–95.1%]. By logistic regression analysis, simultaneous or pre-existent ESBL-GNB colonization was the main risk factor for ESBL-GNB AI (OR = 9.61 [2.86–32.29], $p<0.001$) (Table 4).

Prevalence of ESBL-GNB

Taking into account 131 patients who were colonized at admission, 59 patients who acquired colonization in the ICU and 7 non-colonized patients who acquired ESBL-GNB infection, the overall prevalence rate of ESBL-GNB in was 6.1% [5.2%–6.9%] and varied from 4% to 7.5% between ICUs (Supplementary Table 1).

Micro-organisms identified in acquired infections and antimicrobial susceptibility

The microorganisms and antimicrobial susceptibility are shown in Table 5. In non-ESBL microorganisms, GNB (55%) were the most frequent (*Enterobacteriaceae*, 32.4%;

Pseudomonas aeruginosa, 17.8%). Aerobic GNB were mostly susceptible to all tested antimicrobials, without any major difference between 3rd-generation cephalosporins and imipenem.

All ESBL-GNB responsible for AIs were susceptible to amikacin and imipenem. In 13 of the 15 patients (86.7%) with ESBL-GNB AI, antimicrobial therapy was considered to be appropriate. Among 129 colonization isolates tested, all were susceptible to amikacin and only 3 (two *Pseudomonas aeruginosa* and one *Klebsiella pneumoniae*) were resistant to imipenem (supplementary Table 2).

DISCUSSION

The ESBL-GNB prevalence rate has ranged from 5.7% to 48.0% (7, 14,15,18-22). In a recent meta-analysis, Detsis et al. (18) reported the rate of ESBL-GNB acquired colonization in 13 studies and the ESBL-GNB prevalence rate could be calculated in 10. This review suggests that a low prevalence rate is below 10 % (15, 20, 21), intermediate rate is 10%-20% and high rate is above 20% (18-20).

The main finding of this study was that very few patients (0.46%) acquired ESBL-GNB AIs in ICUs with low prevalence rate of resistance. Prior or simultaneous ESBL-GNB colonization was a strong risk factor for ESBL-GNB AI. This is consistent with other studies with either low (15) or high (19) ESBL-GNB prevalence rate. In patients with suspected or confirmed infection, the relative risk for the ESBL-GNB etiology after prior colonization with ESBL-GNB has been diversely assessed depending on local epidemiology. Houard et al. (19) reported a relative risk of 2.6 [1.2–5.6] in an ICU with ESBL-GNB prevalence rate of 48%. In contrast, Bruyère et al. (15) found a much higher risk (77.5 [23.7–253.4]) in ICUs with a prevalence rate of 7.3%. In our study, the relative risk was not as high (6.6 [2.2–17.6]). Differences were were due to the lower rate of ESBL-GNB AI in non-colonized patients reported by Bruyère (0.6% versus 4.8% in our study), also explaining the higher negative predictive value of prior colonization in this study (99.5% versus 95.2% in our study).

Another important finding in our study was that the majority of ESBL-GNB AIs occurred in non-colonized patients, suggesting an exogenous cause of AI in some cases. ESBL-GNB infection in non-colonized patients has been reported previously with various rates. Jalalzaï et al. observed exogenous infection in 2 of 6 ESBL-GNB AIs (14), Bruyère et al. in 3 among 20 ESBL-GNB AIs (15) while Prevel et al. reported no infection in non-colonized patients during a 6-months study (22). The exogenous source of multi-drug resistant GNB has been examined in the study of Harris et al. (23). From 1806 previously non-colonized patients, the authors reported 27 patients with ESBL-producing *Klebsiella pneumonia* acquisition among whom there were 14 patients (52%) with an isolate similar by molecular typing to an isolate from another patient with an overlapping length of stay in the hospital. The authors suggest that patient-to-patient transmission is an important and underappreciated cause of ESBL-producing *Klebsiella pneumonia* infection and colonization (23). In contrast, Tschudin et al. reported that only 1.5% of acquired colonization was due to patient-to-patient transmission (24). An environmental contamination as a reservoir for ESBL-GNB colonization has recently been emphasized for *Klebsiella pneumoniae* (25).
We observed that admission to ICU 1 was protective for ESBL-GNB acquisition. A major difference between ICU 1 and ICUs 2 and 3 was the use of MSD in intubated patients. The benefit of selective decontamination regimens on acquired colonization with multidrug-resistant Gram-negative bacilli has been shown in France (26) as in other European countries (27). However, selective digestive decontamination does not prevent patient-to-patient cross-transmission.

Recent recommendations support a large panel of antibiotics from ceftriaxone to carbapenems in patients with ICU-acquired pneumonia (28). However, antimicrobial use should be based on local antimicrobial susceptibility surveillance data. Taking into account the high negative predictive value of ESBL-GNB colonization for the prediction of ESBL-GNB AI and high $3^{rd}/4^{th}$ generation susceptibility rate, we suggest that non-carbapenem β-lactams could be safely used in non-colonized patients with AIs in ICUs with low ESBL-GNB prevalence rate. In ESBL-GNB colonized patients, because one third of AIs were caused by ESBL-GNB and all isolates were susceptible to amikacin, we propose that amikacin to be added to a beta-lactam agent.

There were several limitations to our study. First, due to the low number of ESBL-GNB AI, other risk factors may not have been identified. Second, antimicrobial therapy of AIs was not recorded and the impact of the use of broad-spectrum antimicrobials on the incidence of ESBL-GNB AIs could not be assessed. Third, due to the intermittent character of ESBL-GNB screening, transient colonization could have been missed.

In conclusion, in ICUs with low prevalence rate of ESBL-GNB, few ESBL-GNB AIs were reported and prior or simultaneous ESBL-GNB colonization was a major risk factor for infection. In order to treat a suspected pneumonia or BSI acquired in the ICU, our data suggests that carbapenems could be avoided in non-colonized patients and amikacin combination could be used in patients colonized with ESBL-GNB.

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Compliance with Ethical Standards:

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Conflict of interest: The authors declare that they have no conflict of interest for this study.

Ethical approval: The local ethic committee ("comité d'éthique du CHU de rennes") approved the protocol (n°18.56).

Informed consent: This observational retrospective study respects the French reference method MR003. Patients were informed of the study and non-opposition was needed. By the French law, there is no need for patient's written approval.

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Caption Fig.1

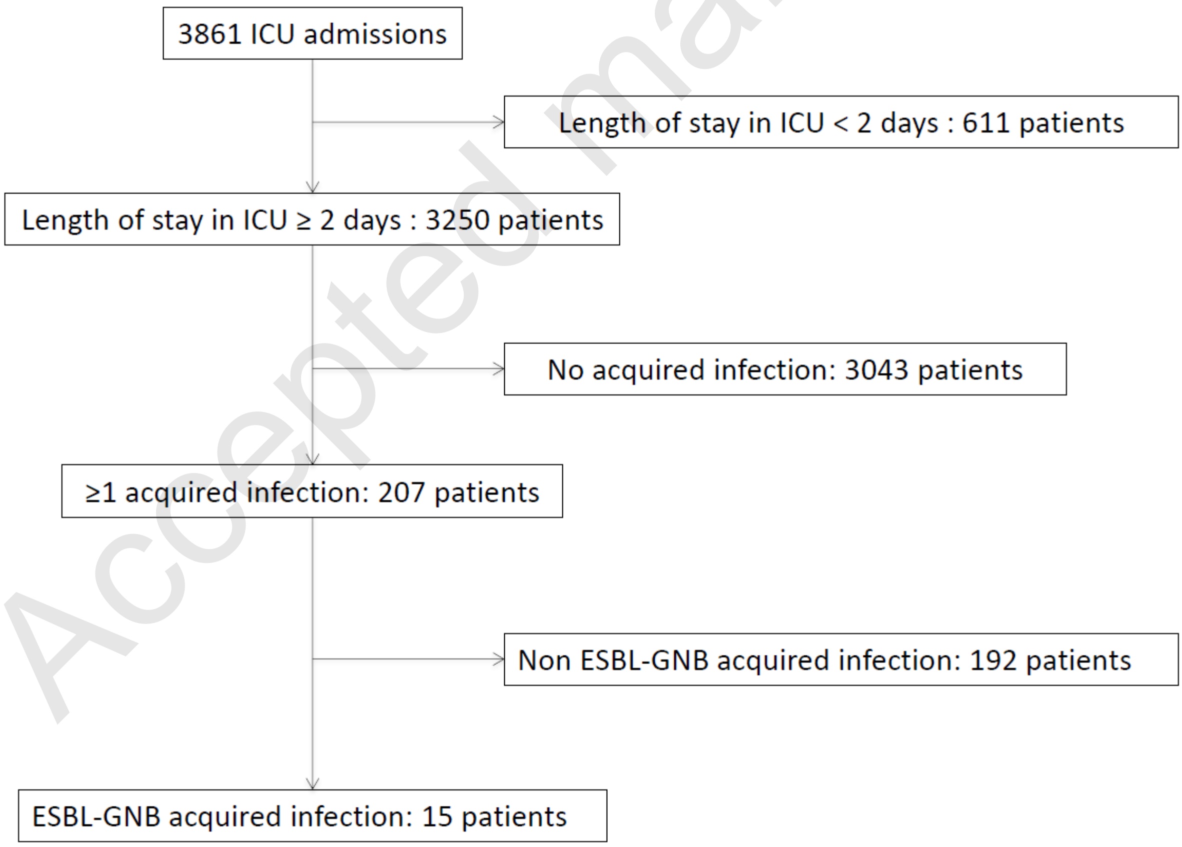

Table 1. Baseline characteristics and outcome of study patients.

	All patients n = 3250	Patients never colonized with ESBL-GNB n = 3060	Patients colonized with ESBL-GNB at admission n = 131	Patients with acquired ESBL-GNB colonization n = 59	Patients with non ESBL-GNB acquired infection n = 192	Patients with ESBL-GNB acquired infection n = 15
Age, years [IQR]	62.1 [51.0 – 71.0]	62.0 [50.0 – 70.9]	65.8 [56.0 – 72.0]	66.0 [56.3 – 75.0]	64.8 [55.0 – 71.5]	70.7 [64.5 – 75.5]
Simplified acute physiology score II [IQR]	40 [28 – 56]	39 [28 – 55.0]	46 [3 3– 58]	48 [34 – 62]	51 [38 – 64]	61 [46 – 67]
Reason for admission – no. (%)						
Surgical	443 (13.6)	412 (13.5)	17 (13.9)	13 (22.0)	33 (17.2)	2 (13.3)
Medical	2445 (75.2)	2346 (76.6)	105 (80.2)	41 (69.5)	132 (68.8)	13 (86.6)
Not precised	362 (11.1)	302 (9.9)	9 (6.9)	5 (8.5)	27 (14.1)	–
Male – no. (%)	2074 (63.8)	1936 (63.3)	92 (70.2)	45 (76.3)	144 (75.0)	12 (80.0)
ESBL- GNB colonization at admission – no. (%)	131 (4.0)	0	131 (100)	–	3 (1.6)	4 (26.6)
ESBL- GNB acquired colonization – no. (%)	59 (1.8)	–	–	59 (100)	10 (5.2)	4 (26.7) §
Days after admission, days [IQR]*	7 [5-14]	–	–	7 [5-14]	14 [11-25]	10 [8-14]
ESBL- GNB acquired infection – no. (%)	15 (0.5)	7 (0.2)	4 (3.1)	4 (6.8) §	–	15 (100)
Intubation duration > 48 hours, – no. (%)	1507 (46.4)	1395 (45.6)	61 (46.6)	51 (86.4)	163 (84.9)	13 (86.6)
Length of stay in ICU, days [IQR]	4 [3 – 9]	4 [2 – 8]	5 [3 – 9]	16 [9 – 33]	20 [9 – 35]	25 [12 – 41]
Death in ICU– no. (%)	645 (19.8)	596 (19.5)	37 (28.2)	12 (20.3)	63 (32.8)	5 (33.3)

Note. ICU : Intensive Care Unit ; ESBL-GNB : extended-spectrum beta-lactamase-producing Gram-negative bacilli. * In patients with acquired colonization only.

Table 2. Risk factors for acquired colonization with extended-spectrum β-lactamase-producing Gram-negative bacilli.

Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age > 65 years	1.33	0.80 – 2.23	0.27			
Simplified Acute Physiology Score II > 40	1.97	1.15 – 3.40	0.014	1.31	0.71 - 2.38	0.38
Male	1.77	0.97 – 3.25	0.06	1.47	0.79 - 2.73	0.22
Surgical reason for admission	1.81	0.96 – 3.40	0.07	1.80	0.91 - 3.31	0.09
Intubation duration > 48 hours	6.62	3.24 – 13.50	< 0.001	4.80	2.26 - 10.24	< 0.001
Admission in ICU 1	0.33	0.19 - 0.58	< 0.001	0.39	0.22 - 0.70	0.002

Note. OR : odds ratio. 95% CI : 95 percent confidence interval.

Table 3. Characteristics of infection due to extended-spectrum β-lactamase-producing Gram-negative bacilli acquired infection.

	Total	Previously colonized patients	Non-previously colonized patients
Number	15	6	9
Delay of onset, days *	9 [2 – 44]	9 [2 – 22]	8 [2 – 44]
Pneumonia – no. (%)	8 (53.3)	3 (50.0)	5 (55.5)
Bloodstream infection – no. (%)	7 (46.6)	3 (50.0)	4 (44.4)
Death in ICU – no. (%)	5 (33.3)	2 (33.3)	3 (33.3)

Note. ICU: Intensive Care Unit. *Results are expressed with median and [minimal – maximal]

Table 4: Risk factors for extended spectrum β-lactamase-producing Gram-negative bacilli acquired infection in 207 patients with acquired infection.

Variable	Univariate			Multivariate		
	OR	95% CI	P-value	OR	95% CI	P-value
Age > 65 years	2.99	0.92 – 9.72	0.07	3.17	0.92 – 10.87	0.07
Simplified Acute Physiology Score II > 40	1.82	0.49 – 6.68	0.90			
Male	1.35	0.36 – 4.96	0.44			
Surgical reason for admission	0.82	0.17 – 3.85	0.80			
Intubation duration > 48 hours	1.16	0.25 – 5.40	0.85			
ESBL-GNB colonization	9.18	2.83 – 29.77	<0.001	9.61	2.86 – 32.29	<0.001

Note. 95% CI: 95 percent confidence interval; ESBL-GNB : extended spectrum β-lactamase-producing Gram negative bacilli.

Table 5: Microorganisms involved in 219 acquired infections and antimicrobial susceptibility.

Micro-organisms	Number of isolates	Antimicrobials: no. susceptible/no. tested (%)						
		Any non-carbapenem β-lactam	Cefepime	Ceftazidime	Piperacillin-tazobactam	Imipenem	Amikacin	Methicillin
Non-ESBL producing microorganisms								
Enterobacteriaceae	69	52/53 (98.1)	49/50 (98.0)	47/50 (94.0)	44/53 (83.0)	53/55 (96.4)	37/41 (90.2)	-
Pseudomonas aeruginosa	38	35/38 (92.1)	34/38 (89.5)	34/38 (89.5)	35/38 (92.1)	35/38 (92.1)	37/38 (97.4)	-
Acinteobacter species	6	5/6 (83.3)	5/6 (83.3)	5/6 (83.3)	5/6 (83.3)	5/6 (83.3)	5/6 (83.3)	-
Anaerobes	5	4/4 (100)	-	-	4/4 (100)	-	-	-
Staphylococcus aureus	35	-	-	-	-	-	-	32/35 (91.4)
Coagulase negative *Staphylococcus*	32	-	-	-	-	-	-	13/28 (46.4)
Streptococcus species	14	-	-	-	-	-	-	-
*Enterococcus species**	6	-	-	-	-	-	-	-
Others	8	-	-	0/1	0/1	1/1 (100)	1/2 (50.0)	-
Total	213	96/101 (95.0)	88/94 (93.6)	86/95 (90.5)	88/102 (86.3)	94/100 (94.0)	80/87 (91.9)	45/63 (71.4)
ESBL-GNB								
E. coli	8	5/8 (62.5)	-	1/8 (12.5)	5/8 (62.5)	8/8 (100)	8/8 (100)	-
Enterobacter cloacae	4	1/4 (25.0)	-	0/4	1/4 (25.0)	4/4 (100)	4/4 (100)	-
Klebsiella pneumoniae	3	2/3 (66.6)	-	0/3	2/3 (66.6)	3/3 (100)	3/3 (100)	-
Total	15	8/15 (53.3)	-	1/15 (6.7)	8/15 (53.3)	15/15 (100)	15/15(100)	-

Note. ESBL-GNB : extended-spectrum beta-lactamase-producing Gram-negative bacilli. * no glycopeptide resistant enterococcus was isolated.