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ET DE LA GUYANE
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HYACINTHE BASTARAUD
N°2019ANTI0427

Thèse pour l'obtention

De Doctorat en Médecine

**Epidemiology and prognosis of intensive care unit
acquired blood stream infection in French Guiana**

Présentée et soutenue
Le 20 Novembre 2019

Par

Michaela ROY

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La vie n'est pas un long fleuve tranquille,
Le bonheur se trouve là où on l'attend le moins.

Liste des abréviations

ICU = intensive care unit

BSI= bloodstream infections

HCA= health care acquired

CA= community acquired

SOFA= sequential organ failure assessment

ESBL-E = extended spectrum b lactamase producing *Enterobacteriaceae*

CI= confidential interval

FG= French Guiana

LOS= length of stay

MDR-B= multi drug resistant bacteria

Pyo CAZ-R= *Pseudomonas aeruginosa* resistant to Ceftazidime

ABB= *Acinetobacter baumannii*

CRE= carbapenem-resistant *Enterobacteriaceae*

STM= *Stenotrophomonas maltophilia*

MRSA= methicillin-résistant *Staphylococcus aureus*

ABRI= *Acinetobacter baumannii* resistant to imipenem

CVC= central venous catheter

AC= arterial catheter

MV= mechanical ventilation

RRT= renal replacement therapy

ROC= receiver operating characteristic

VAP= ventilator associated pneumonia

ATB= antibiotics

AMX-Clav= Amoxicillin-clavulanate

PIP-TAZ= Piperacillin tazobactam

3rd GC= Third generation cephalosporins

IMI= imipenem

Summary

INTRODUCTION

Intensive care unit acquired blood stream infections(ICU-BSI) are frequent,and associated with high morbidity and mortality rates.

The objective of our study was to describe the epidemiology and the prognosis of ICU-BSI in our ICU (Cayenne General Hospital). Secondary objectives were to search for factors associated to ICU-BSI caused by ESBL-PE ,the impact of ESBL-PE carriage on the incidence of ICU-BSI caused by ESBL-PE and factors associated with mortality at 28 days.

METHODS

We retrospectively studied ICU-BSI in the medical-surgical intensive care unit of the Cayenne General Hospital, during 78 months (January 2013 to June 2019). We assessed survival at 28daysfrom the diagnosis of ICU-BSI.

RESULTS

ICU-BSI was diagnosed in 9.5% of admissions giving a density incidence of 10.3 ICU-BSI/1000 days.

The median delay to the first positive bacteraemia was 9 days.

The ICU-BSI was primitive in44% of cases and secondary to ventilator acquired pneumonia in 25% of cases.

One microorganism was isolated in 82.1% and two in 17,9% of cases.The main isolated microorganism were Enterobacteriaceae in 67.7% of patients. They were ESBL-producers in 27.6% of cases.

Initial antibiotic therapy was appropriate in 65.1% of cases.

Factors independently associated with ESBL-PE as the causative microorganism of ICU-BSI were ESBL-PE carriage prior to ICU-BSI (OR: 7.273; 95%CI: 2.876-18.392; $p<0.000$) and prior exposure to fluoroquinolones (OR: 4.327; 95%CI: 1.120-16.728; $p=0.034$).

The sensitivity of ESBL-PE carriage to predict ESBL-PE as the causative microorganism of ICU-BSI was 64.9%, and specificity was 81.2%.

Mortality at 28 days was 20.6% in the general population. In ESBL-PE carriers, it was 19.4% in ICU-BSI caused ESBL-PE and 14.1% in ICU-BSI caused by non ESBL-PE ($p=ns$).

The median ICU length of stay was 26 days (15-49). It was 35 days (20-61) in ESBL-PE carriers, 38 days (20-60) in ESBL-PE carriers with ICU-BSI caused by ESBL-PE vs 35 days (21-64) in ESBL-PE carriers with ICU-BSI caused by non ESBL-PE ($p=ns$).

In Multivariable analysis, factors independently associated with mortality at day 28 from the occurrence of ICU-BSI were traumatic category of admission (OR: 0.346; 95%CI: 0.134-0.894; $p=0.028$) and septic shock associated to ICU-BSI (OR: 3.317; 95%CI: 1.561-7.050; $p=0.002$).

CONCLUSIONS

ICU-BSI complicates9.5% of admission to ICU and was associated with 25% in-hospital mortality. Associated prognosis factors were non traumatic category at admission and septic shock the day of the ICU-BSI.

Résumé

INTRODUCTION

Les infections sanguines en réanimation (ISR) sont fréquentes et associées à des taux de morbidité et de mortalité élevés.

L'objectif de notre étude était de décrire l'épidémiologie et le pronostic des ISR dans notre service (centre Hospitalier de Cayenne). Les objectifs secondaires étaient de chercher des facteurs associés aux ISR causés par une entérobactérie sécrétrice de BLSE (E BLSE), l'impact du portage des E BLSE sur l'incidence des ISR à E BLSE, et les facteurs associés à une mortalité à 28 jours.

METHODES

Nous avons étudié rétrospectivement les ISR dans le service de réanimation de Cayenne, pendant une période de 78 mois (janvier 2013 à juin 2019).

Nous avons évalué la survie à 28 jours à compter du diagnostic de la BAR.

RÉSULTATS

Une ISR a été diagnostiquée chez 9,5% des patients hospitalisés pendant la période de l'étude. La densité d'incidence était de 10,3 ISR / 1000 jours d'hospitalisation.

Le délai médian avant la première ISR était de 9 jours. La ISR était primitive dans 44% des cas et secondaire à une pneumonie acquise sous ventilation mécanique dans 25% des cas.

Un seul microorganisme a été isolé dans 82,1% des cas et deux dans 17,9% des cas.

Les principaux microorganismes isolés étaient des Enterobacteries chez 67,7% des patients. Elles étaient productrices de BLSE (EP-BLSE) dans 27,6% des cas. L'antibiothérapie initiale était appropriée dans 65,1% des cas.

Les facteurs indépendants associés à des EP-BLSE en tant que micro-organisme causal des ISR étaient un antécédent de portage d'une EP-BLSE avant le diagnostic de la ISR (OR: 7,273; IC 95%: 2,876-18,392; $p < 0,000$) et une exposition antérieure aux fluoroquinolones (OR: 4.327; IC 95%: 1,120-16,728; $p = 0,034$).

La sensibilité du portage d'une EP-BLSE à prédire une EP-BLSE comme microorganisme responsable de la ISR était de 64,9% et sa spécificité était de 81,2%.

La mortalité à 28 jours était de 20,6% dans la population générale.

Chez les patients colonisés à EP-BLSE, elle était de 19,4% en cas de ISR causée par une EP-BLSE et de 14,1% en cas de ISR non causée par une EP-BLSE ($p = ns$).

La durée médiane de séjour en réanimation était de 26 jours (15 - 49).

Elle était de 35 jours (20-61) chez les patients porteurs d'EP-BLSE, 38 jours (20-60) chez les porteurs d'EP-BLSE avec une ISR causée par EP-BLSE vs 35 jours (21-64) chez les porteurs d'EP-BLSE avec une ISR non causée par EP-BLSE ($p = ns$).

En analyse multivariée, les facteurs indépendants liés à la mortalité à J28 étaient la catégorie traumatique à l'admission (OR: 0.346; CI95%: 0.134-0.894; $p=0.028$) et le choc septique le jour de l'ISR (OR: 3.317; CI95%: 1.561-7.050; $p=0.002$).

CONCLUSIONS

Les BAR compliquent 9,5% des admissions en réanimation et sont associées à 25% de mortalité. Les facteurs indépendants associés à la mortalité à J28 étaient la catégorie non traumatique à l'admission et le choc septique le jour de l'ISR.

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Introduction

Bloodstream infections (BSIs) are a frequent, life-threatening condition in hospital settings [1], and are responsible of an increased burden and cost [2]. They represent the third-most commonly recorded infection in intensive care units (ICUs)[3]. Indeed, BSI occur in approximately 5 to 15% of all patients within the first month of hospitalization in ICU [4,5], with an incidence rate between 5 and 19 per 1000 patient days [6].

BSIs caused by multidrug resistant bacteria is considered a public health problem worldwide[7–9]. They represent an additional burden of disease with higher mortality, longer ICU stay, longer delay in starting effective antimicrobials and higher costs rather than BSIs caused by susceptible bacteria [5,7,10–15]. For this, intensivists should be aware of the main risk factors for BSIs caused by resistant bacteria.

BSIs are associated with particularly high morbidity and mortality rates and are marker of adverse outcome. The case fatality rate associated with BSIs is 15-20%. It raises to 35-50% in case of organ failures[5,7,15–18]. In the global population, BSI accounts for 1% excess mortality, with 5% of attributed death in ICU[4]. BSIs also increases the length of ICU-stay and healthcare-related costs [19].

Some factors such as the source of infection, the severity of illness, the causal pathogen and its susceptibility profile, can impact the associated mortality to ICU acquired BSI (ICU-BSI). Indeed, infections due to extended spectrum beta-lactamase producer enterobacteriaceae (ESBL-PE) are associated with impaired outcome compared to infections with susceptible pathogens probably because of inadequate empirical therapy [20]. Indeed, the delay of adequate antimicrobial chemotherapy in case of ESBL-PE BSIs can be an important factor linked to mortality [21].

Early and appropriate antibiotic therapy after blood cultures is an important issue in patients with ICU-BSI. It require that all organisms isolated from blood are susceptible in vitro to the antimicrobials chosen with a proper route of administration and dose [9,22]. It has demonstrated to reduce mortality and to improve clinical outcomes, particularly in severe

patients [23]. However, this relationship is controversial and treatment adequacy sometimes was unrelated to outcomes[24].

Objectives:

The principal objective of our study is to describe the epidemiology and the impact on outcome of ICU-BSI in our ICU (Cayenne General Hospital)

The secondary objectives are to search for:

- ✓ factors associated to ICU-BSI caused by ESBL-PE
- ✓ impact of ESBL-PE carriage on the incidence of ICU-BSI caused by ESBL-PE
- ✓ factors associated with severe outcome which is defined as the mortality at 28 days from the diagnosis of ICU-BSI

Materials and methods

1. Setting and patients

Our study is retrospective. It was conducted over 78-month period (6.5 years, from January 2013 to June 2019) in the medical-surgical intensive care unit of the Cayenne General Hospital. Our hospital is a 510-bed general center that serves as first-line medical center for an urban population of 150,000 inhabitants and as a referral center (with the only ICU in the region) for a larger population coming from all French Guiana. Our ICU comprises 8 single and 3 double-bed rooms with a 1: 2.5 nurse-to-patient ratio. All patients have dedicated equipment for care and monitoring. Hand hygiene is based on alcohol hand rub (at room entrance and exit, and between each distinct procedure of care), and the use of single-use gloves and gowns in case of close contact with patients and potential exposure to body fluids during nursing.

Cayenne is the regional capital of French Guiana, which is a French territory located on the North Atlantic coast of South America. It has borders with Brazil and Suriname. Its area is 83,534 square kilometers, with an estimated population of 254,000 people in 2014. French Guiana is home to many unique and important ecosystems. Equatorial rainforests cover 95% of the territory and expose to a wide range of various infectious diseases.

We included all patients hospitalized in our ICU and who had acquired bloodstream infection (BSI) during their ICU stay (ICU-BSI). For patients who were readmitted to ICU, we included all patients with a first ICU admission during the same hospital stay. Patients hospitalized in 2012 and present in the unit in the 1/1/2013, were considered as admitted the 1/1/2013. In the analysis, we included the first episode of ICU-BSI.

Screening for multi-drug resistant bacteria (MDR-B) carriage was performed according to the French Society of Hospital Hygiene (SFHH) recommendations [25]. Patients are routinely screened on ICU admission and then, weekly during the ICU stay. ESBL production was confirmed by the double-disk diffusion method using ceftazidime or cefotaxime with clavulanic acid [26]. Contact precautions are used for patients with MDR bacteria recovered from screening cultures according to the SFHH recommendations [25].

Blood cultures were performed using aerobic (Bact/ALERT FA plus) and anaerobic (Bact/ALERT FN plus) blood culture vials incubated in a BacT/ALERT 3D (bioMérieux,

Marcy l'Etoile, France). The positive blood culture vials were subcultured on blood and chocolate Polyvitex agar plates. All isolates were then identified using MALDI-TOF mass spectrometry (MaldiBiotyper 3.0, Bruker Daltonique, Marnes la Vallée, France).

Antimicrobial susceptibility testing was carried out using the agar disk diffusion method (Bio-Rad) or an automated broth microdilution method (Phoenix, BD Diagnostics, Oxford, UK).

The breakpoints used were those defined by the French Committee for Antimicrobial Susceptibility Testing

(http://www.sfmmicrobiologie.org/UserFiles/files/casfm/CASFM%20V1_0%20FEV_2018.pdf).

2. Data collection

Medical charts were reviewed using a standardized data set to collect demographic characteristics; clinical, biological, microbiological data, and outcomes of each patient.

The following data were collected: demographic characteristics, which included sex, age, type of admission, simplified acute physiology score (SAPS II) [6], organ dysfunction at admission (acute change in total SOFA score ≥ 2 points) [27], location before ICU admission, main reason for admission, hospitalization and administration of antibiotics in the previous year (stratified according to receipt within 6 months or 3 months of admission or earlier), presence of underlying diseases, exposure to central venous or arterial catheterization (CVC, AC), mechanical ventilation (MV), renal replacement therapy (RRT), and antibiotics during hospitalization in ICU, MDR-B carriage including ESBL-PE carriage, ICU-acquired infections, length of ICU stay, and outcome at discharge from ICU.

Our database has been registered at the Commission National de l'Informatique et des Libertés (registration n° 2209669), in compliance with French law on electronic data sources.

3. Definitions

MDR-B carriage was defined as the isolation of MDR-B from a surveillance culture or non-sterile clinical sample. Patients with MDR-B isolated within 48 hours of ICU admission were considered to be colonized upon admission. MDR-B isolated 48 hours after admission in patients with previous negative specimens were considered as ICU-acquired [28].

Infections were defined according to the Center for Disease Control (CDC) definitions [29].

ICU-BSI was defined by an infection onset occurring at least 48 h after ICU admission, with 1 positive blood culture unrelated to an infection incubating at ICU admission. Coagulase-negative *Staphylococcus* bacteraemia was defined by 2 blood cultures showing the same phenotype on separate occasions within a 48 h period, or at least 1 blood culture positive for clinical sepsis, no other infectious process, and antibacterial agent treatment initiated by the attending physician [30]. In the absence of a known source, ICU-BSI was classified as primary. Secondary BSI was defined by the recovery of the same microorganism from 1 blood culture and from a suspected source. All catheter-related infections were documented by quantitative tip culture [31]. The day of the appropriate antimicrobial therapy initiation was recorded.

Prior antibiotic exposure in ICU was defined as the use of at least 1 dose of any antimicrobial treatment from admission until the day before ICU-BSI.

Immunosuppression included the following: diabetes mellitus, ongoing neoplasia, hemopathy, HIV, hypogammaglobulinemia, immunosuppressive therapy (ie. corticotherapy > 20 mg/d, chemotherapy or immunosuppressive treatment such as cyclophosphamide, azathioprine and cyclosporine).

The primary site of infection was clinically suspected and bacteriologically documented with the same bacterial identification as that in the blood culture.

4. Statistical analysis

Results are reported as median and interquartile range (25th–75th percentiles), or numbers with percentages.

Initial bivariate statistical comparisons were conducted using the Chi-square or Fisher's exact test for categorical data and the Mann–Whitney *U* test for continuous data. To compare subgroups, we used multivariable logistic regression with a backward procedure. Non-redundant variables selected by bivariate analysis ($p < 0.05$) and considered clinically relevant were entered into a logistic regression model.

Results are expressed as crude and adjusted odds ratios (OR) with their 95% confidence intervals (CI). A p value <0.05 was considered statistically significant.

We calculated the sensitivity, specificity, positive and negative predictive values, Youden test and the Q coefficient of Yule to assess the diagnosis value of the diagnosis tests.

All statistical analyses were carried out with Excel (2007) and Statistical Package for the Social Sciences (SPSS) program (Version 24).

Results

During the study period, we recorded 2353 admissions resulting in 28627 days of hospitalization in intensive Care Unit. Among them, 223 (9.5%) developed ICU-BSI and were included in our study. The median number of ICU-BSI was 29 cases per year (IQR: 26-37) (Figure 1). The total number of days of hospitalization without ICU-BSI was 21706 days giving a density of incidence of 10.3 ICU-BSI/1000 days of hospitalization. The monthly analysis showed a median density of incidence of 6.9 ICU-BSI /1000 days of hospitalization (IQR: 3.8-11.2) (Figure 2).

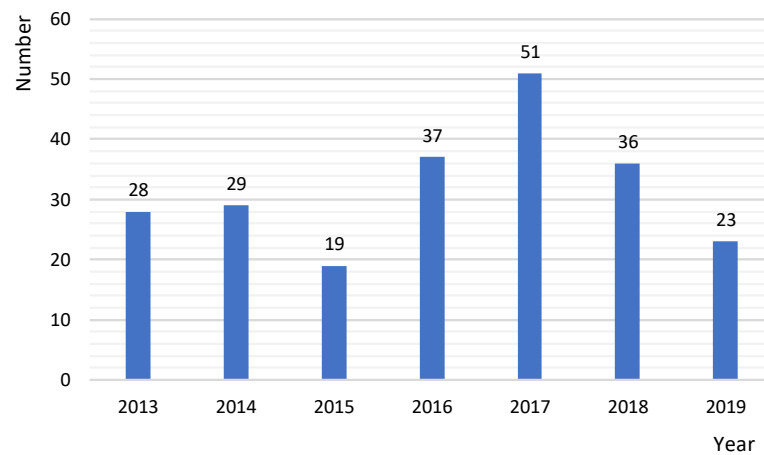


Figure 1: The incidence of ICU-BSI according to the year of the study.

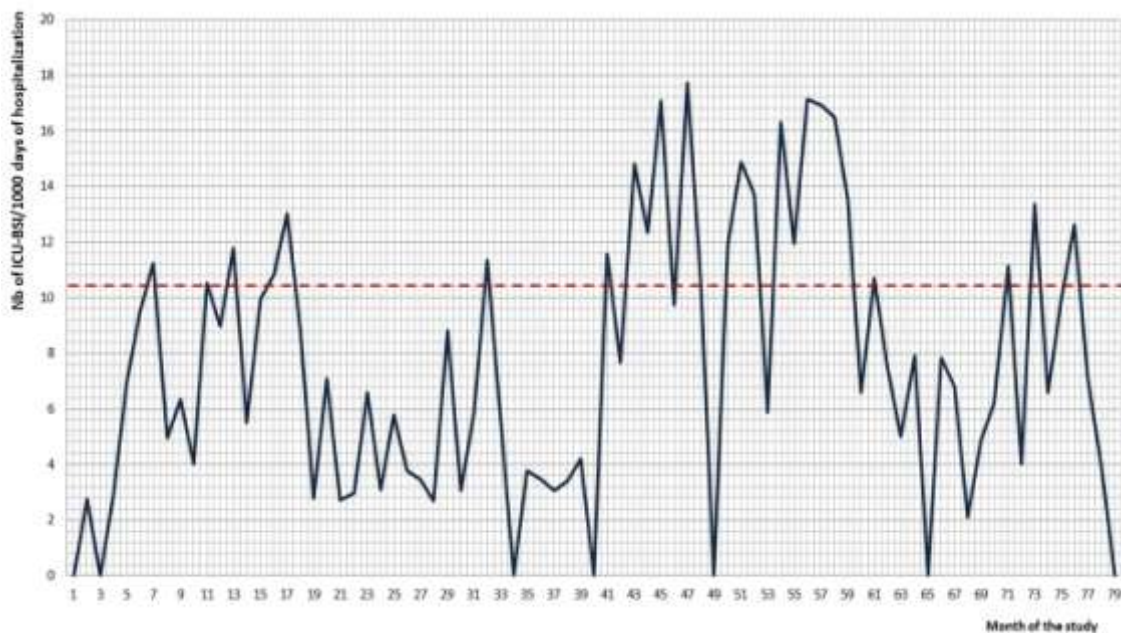


Figure 2: The monthly analysis of the number of ICU-BSI /1000 days of hospitalization.

1. The study population

The median age of our patients was 49 years (IQR: 35 - 61) and 67.3 % of them were men. One or more comorbidity was recorded in 57.8 % of patients. Immunodeficiency was recorded in 17.9% of patients and HIV infection was the main immunodeficiency origin. Epidemiological and clinical characteristics of all patients at admission to ICU are reported in Table I.

Table I: Epidemiologic and clinical characteristics of the study population

Variable	Nb	Result
Age, years	223	49 (35 - 61)
Male gender	223	150 (67.3%)
BMI	191	25 (22 – 30)
SAPS II	219	50 (40 - 64)
Comorbidities	223	129 (57.8%)
Arterial hypertension	223	71 (31.8%)
Diabetes mellitus	223	29 (13%)
Cancer	223	9 (4%)
Immunodeficiency	223	40 (17.9%)
Chronic renal failure	223	11 (4.9%)
Chronic respiratory failure	223	4 (1.8%)
Sickle cell disease	223	10 (4.5%)
Type of admission		
Medical	223	158 (70.9%)
Elective surgery	223	0
Emergent surgery	223	66 (29.1%)
Traumatic	223	68 (30.5%)
ATB during previous year	223	27 (12.1%)
In the last 3 months	223	18 (8.1%)
In the last 3 to 6 months	223	5 (2.2%)
In the last 6 to 12 months	223	4 (1.8%)
Hospitalization during previous year	223	44 (19.1%)
In the last 3 months	223	21 (9.4%)
In the last 3 to 6 months	223	6 (2.7%)
In the last 6 to 12 months	223	17 (7.6%)

2. Active infection at admission to ICU

Active infection at admission was recorded in 117 patients (52.5%) and associated bloodstream infection was recorded in 23 of them (19.7%). Antibiotics were prescribed in 69.1% of patients at admission to ICU. The sites of active infection diagnosed at admission to ICU are reported in Table II and antibiotics prescribed at admission are listed in table III.

Table II: The sites of active infection diagnosed at admission to ICU

Site of infection	Associated BSI		Total
	No	Yes	
Pulmonary	68 (95.8%)	3 (4.2%)	71 (100%)
Intra-abdominal	10 (66.7%)	5 (33.3%)	15 (100%)
Cellulitis	6 (100%)	0	6 (100%)
Neuro-meningeal	6 (66.7%)	3 (33.3%)	9 (100%)
Urinary	3 (42.9%)	4 (57.1%)	7 (100%)
Catheter related infection	1 (100%)	0	1 (100%)
Endocarditis	0	1 (100%)	1 (100%)
Primary BSI	0	7 (100%)	7 (100%)
Total	94 (80.3%)	23 (19.7%)	117 (100%)

Table III: Antibiotics prescribed at admission

Antibiotic	Nb	Result
Antibiotics at admission	223	154 (69.1%)
Amoxicillin-clavulanate	223	70 (31.4%)
Aminoglycosides	223	31 (13.9%)
Piperacillin-Tazobactam	223	35 (15.7%)
3rd generation cephalosporins	223	34 (15.2%)
Imipenem	223	10 (4.5%)
Fluoroquinolones	223	10 (4.5%)
Metronidazole	223	3 (1.3%)

3. Therapeutic management during hospitalization in ICU

During ICU stay, 92.8% of patients received invasive mechanical ventilation, 19.3% received renal replacement therapy (RRT), 96.5% had central venous catheterization, and 92.4% had arterial catheterization. Antibiotic exposure during ICU stay was recorded in 92.4% of patients. Therapeutic procedures and antibiotics exposure during hospitalization in ICU are reported in Table IV.

Table IV: Therapeutic management during hospitalization in ICU.

Variable	Nb	Result
Mechanical ventilation	223	207 (92.8%)
Time from admission to MV, days	207	0 (0 - 0)
MV at admission to ICU	207	177 (79.4%)
MV more than 48 hours	207	204 (98.6%)
Duration of MV, days	207	20 (13 - 33)
Overall duration of MV, days	207	6470
Duration of MV without VAP, days	207	3765
Tracheostomy	207	37 (17.9%)
Renal replacement therapy	223	43 (19.3%)
Time from admission to RRT, days	43	1 (0 - 8)
Central venous catheterization	223	216 (96.5%)
Overall duration of CVC, days	216	6382
Duration of CVC without infection, days	216	5495
Arterial catheterization	223	206 (92.4%)
Overall duration of AC, days	206	3948
Duration of AC without infection, days	206	3818
ATB exposure during hospitalization	223	206 (92.4%)

MV: Mechanical Ventilation. VAP: Ventilator Associated Pneumonia. RRT: Renal Replacement Therapy.
AC: Arterial catheterization. CVC: Central Venous Catheter

4. Multidrug-resistant bacteria carriage

One hundred and forty-one patients (63.2%) were MDR-B carriers and 121 patients (54.3%) carried ESBL-PE. Twenty-seven patients (12.1%) were screened positives to ESBL-PE at admission to ICU (Table V). The main ESBL-PE isolated at admission were *K pneumoniae* (40.7% of ESBL-PE carriers at admission) and *E coli* (37% of ESBL-PE carriers at admission). The rates of MDR-B carriage at admission and during ICU stay are reported in Table V.

Table V: Multidrug-resistant bacteria and ESBL-PE carriage in ICU

Variable	Nb	Result
MDR-B carriage	223	141 (63.2%)
ESBL-PE carriage	223	121 (54.3%)
ESBL-PE carriage at admission	223	27 (12.1%)
ESBL-PE carriage acquired in ICU	223	94 (42.2%)

Ninety-four patients acquired ESBL-PE carriage during ICU stay (42.2% of all patients and 47.9% of non ESBL carriers at admission). The main ESBL-PE isolated on rectal swab samples during ICU stay were *K pneumoniae* (in 57 patients, 60.6% of patients acquiring ESBL-PE) and *E cloacae* (in 22 patients, 23.4% of patients acquiring ESBL-PE) (Table VI and Figure 3).

Table VI: ESBL-PE carriage at admission and during ICU stay*

	At admission	ICU acquired	Total
<i>Escherichia coli</i>	10 (52.6%)	9 (47.4%)	19 (100%)
<i>Klebsiella pneumoniae</i>	11 (16.2%)	57 (83.8%)	68 (100%)
<i>Enterobacter cloacae</i>	5 (18.5%)	22 (81.5%)	27 (100%)
<i>Serratia marcescens</i>	1 (16.7%)	5 (83.3%)	6 (100%)
<i>Enterobacter aerogenes</i>	0 (0%)	3 (100%)	3 (100%)
<i>Enterobacter asburiae</i>	1 (50%)	1 (50%)	2 (100%)
<i>Citrobacter freundii</i>	0 (0%)	1 (100%)	1 (100%)
<i>Klebsiella oxytoca</i>	0 (0%)	1 (100%)	1 (100%)
Total	28 (22%)	99 (78%)	127 (100%)

Six patients were carrying 2 ESBL-PE (one at admission and five during ICU stay)

*Only the first ESBL-PE carriage in each patient was reported.

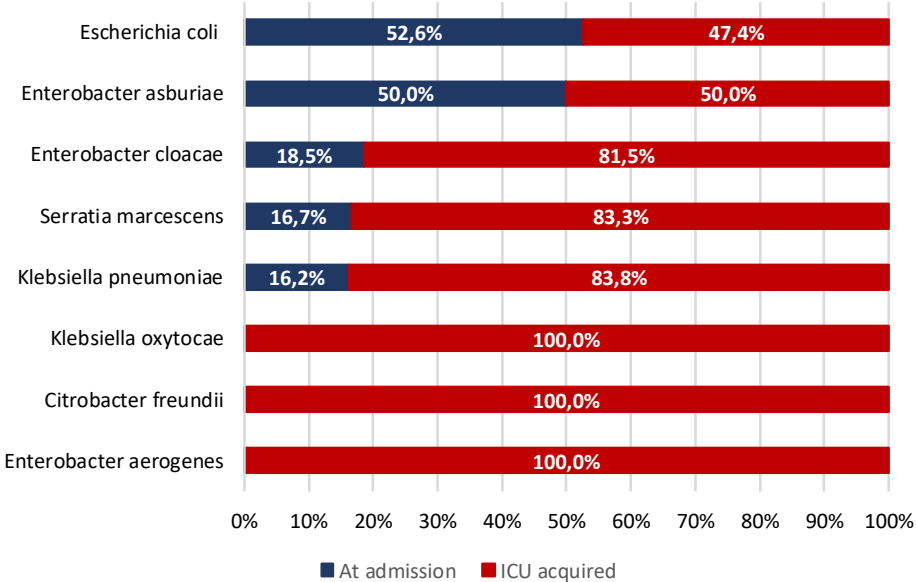


Figure 3: ESBL-PE carriage at admission and during ICU stay

5. Intensive Care Unit Acquired Infection

During ICU stay, we recorded 453 episodes of ICU-AI (Table VII).

Table VII: ICU-AI before and after the studied episode of ICU-BSI

Site of ICU-AI	ICU-AI before the first ICU-BSI	ICU-BSI	ICU-AI after the first ICU-BSI		Total
			Without BSI	With BSI	
Primary BSI	0 (0%)	98 (62.4%)	0 (0%)	59 (37.6%)	157 (100%)
VAP	42 (29,8%)	57 (40.4%)	34 (24.1%)	8 (5.7%)	141 (100%)
Catheter related	9 (10,3%)	39 (44.8%)	15 (17.2%)	24 (27.6%)	87 (100%)
Urine	5 (17,2%)	15 (51.7%)	6 (20.7%)	3 (10.3%)	29 (100%)
Cutaneous	2 (20%)	5 (50%)	1 (10%)	2 (20%)	10 (100%)
Pulmonary	2 (20%)	4 (40%)	3 (30%)	1 (10%)	10 (100%)
Abdominal	0 (0%)	2 (40%)	2 (40%)	1 (20%)	5 (100%)
Endocardial	0 (0%)	2 (100%)	0 (0%)	0 (0%)	2 (100%)
Surgical site infection	0 (0%)	1 (50%)	0 (0%)	1 (50%)	2 (100%)
Bronchitis	1 (50%)	0 (0%)	1 (50%)	0 (0%)	2 (100%)
Gynecologic	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Ophthalmic	1 (100%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)
Bone	1 (33,3%)	0 (0%)	2 (66.7%)	0 (0%)	3 (100%)
Sinusitis	0 (0%)	0 (0%)	1 (100%)	0 (0%)	1 (100%)
Neuromeningeal	0 (0%)	0 (0%)	2 (100%)	0 (0%)	2 (100%)
Total	64	223	67	99	453

6. Antibiotic exposure prior to ICU-BSI

Antibiotic exposure prior to ICU-BSI was observed in 159 patients (71.3%). The main recorded antibiotics were Aminoglycosides (32.7%), Amoxicillin clavulanate (29.1%), and Piperacillin-Tazobactam (25.1%) (Table VIII).

Table VIII: Antibiotic exposure prior to ICU-BSI

Variable	Nb	Result
ATB exposure prior to ICU-BSI	223	159 (71.3%)
Amoxicillin clavulanate	223	65 (29.1%)
Aminoglycosides	223	73 (32.7%)
Piperacillin-Tazobactam	223	56 (25.1%)
3rd generation cephalosporins	223	48 (21.5%)
Imipenem	223	24 (10.8%)
Fluoroquinolones	223	19 (8.5%)
Metronidazole	223	6 (2.7%)

7. Intensive Care Unit Acquired Bloodstream Infection

The duration of hospitalization without ICU-BSI was 9 days (IQR: 5-16). The ICU-BSI was primary in 98 patients (44%) and secondary to an identified source in 125 cases (56%) (Table IX and Figure 4).

Table IX: The source of ICU-BSI

Variable	Nb	Result
Primary BSI	223	98 (44%)
VAP	223	57 (25.6%)
Catheter	223	39 (17.5%)
Urine	223	15 (6.7%)
Cutaneous	223	5 (2.2%)
Pulmonary	223	4 (1.8%)
Abdominal	223	2 (0.9%)
Endocardial	223	2 (0.9%)
Surgical site infection	223	1 (0.4%)

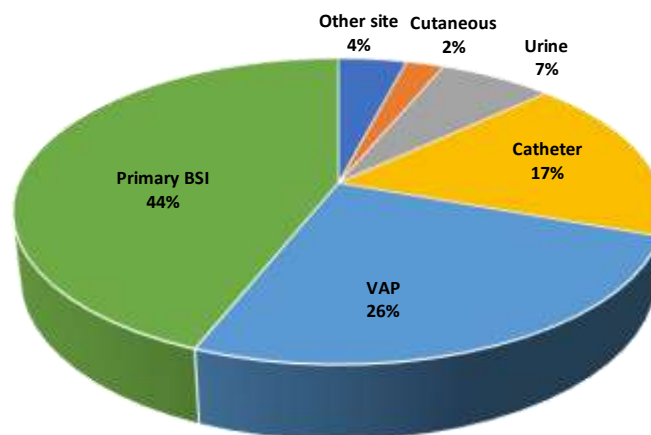


Figure 4 : The source of ICU-BSI

ICU-BSI was caused by one microorganism in 184 cases (82.5%) and two microorganisms in 39 cases (17.5%). The microorganism recovered was an Enterobacteriaceae in 151 patients (67.7%). It was ESBL producer in 37 cases (24.5%). *Candida spp* caused 10 cases (4.5%) of ICU-BSI. In two cases there was coinfection with *Candida spp*. And *K pneumoniae*. The responsible micro-organisms recovered from ICU-BSI are reported in table X. The responsible micro-organisms according to the site of ICU-BSI are reported in Table XI.

Table X: The responsible micro-organisms of ICU-BSI

	Frequency	%organisms	% patients
Gram Positive Cocci	57	22	26
<i>Methicillin-Susceptible Staphylococcus aureus</i>	21	8	9
<i>Coagulase-negative staphylococci</i>	16	6	7
<i>Enterococcus faecalis</i>	10	4	5
<i>Methicillin-resistant Staphylococcus aureus</i>	4	2	2
<i>Streptococcus spp</i>	5	2	2
<i>Enterococcus faecium</i>	1	0	0
Gram negative bacilli	193	74	87
Enterobacteraceae	151	58	68
<i>Klebsiella pneumoniae</i>	65	25	29
<i>Enterobacter cloacae</i>	32	12	14
<i>Escherichia coli</i>	16	6	7
<i>Enterobacter aerogenes</i>	14	5	6
<i>Serratia marcescens</i>	9	3	4
<i>Citrobacter koseri</i>	6	2	3
<i>Enterobacter asburiae</i>	2	1	1
<i>Klebsiella varicola</i>	2	1	1
<i>Proteus mirabilis</i>	1	0	0
<i>Pantoea dispersa</i>	1	0	0
<i>Morganella morganii</i>	1	0	0
<i>Citrobacter yougae</i>	1	0	0
<i>Citrobacter freundii</i>	1	0	0
Non fermentative Gram negative bacilli	42	16	19
<i>Pseudomonas aeruginosa</i>	19	7	9
<i>Acinetobacter baumannii</i>	11	4	5
<i>Acinetobacter nosocomialis</i>	5	2	2
<i>Aeromonas hydrophila</i>	2	1	1
<i>Stenotrophomonas maltophilia</i>	2	1	1
<i>Acinetobacter xylooxidans</i>	1	0	0
<i>Burkholderia cepacia</i>	2	1	1
Candida spp	10	4	5
<i>Candida parapsilosis</i>	5	2	2
<i>Candida albicans</i>	3	1	1
<i>Candida tropicalis</i>	1	0	0
<i>Candida glabrata</i>	1	0	0
Others	2	1	1

Table XI: The responsible micro-organisms according to the site of ICU-BSI

	Primary BSI	VAP	CRBSI	Urinary	Others	Total
Gram positive Cocci	25 (22.1%)	7 (10%)	17 (37.8%)	4 (21.1%)	4 (26.7%)	57 (21.8%)
<i>Staphylococcus aureus</i>	3 (2.7%)	7 (10%)	12 (26.7%)	2 (10.5%)	1 (6.7%)	25 (9.5%)
<i>Coagulase-negative staphylococci</i>	12 (10.6%)	0 (0%)	2 (4.4%)	0 (0%)	2 (13.3%)	16 (6.1%)
<i>Enterococcus faecalis</i>	6 (5.3%)	0 (0%)	2 (4.4%)	1 (5.3%)	1 (6.7%)	10 (3.8%)
<i>Streptococcus Spp</i>	3 (2.7%)	0 (0%)	1 (2.2%)	1 (5.3%)	0 (0%)	5 (1.9%)
<i>Enterococcus faecium</i>	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Gram Negative Bacilli	81 (71.7%)	62 (88.6%)	26 (57.8%)	13 (68.4%)	11 (73.3%)	193 (73.7%)
Enterobacteriaceae	63 (55.8%)	48 (68.6%)	18 (40%)	13 (68.4%)	9 (60%)	151 (57.6%)
<i>Klebsiella pneumoniae</i>	21 (18.6%)	24 (34.3%)	9 (20%)	8 (42.1%)	3 (20%)	65 (24.8%)
<i>Enterobacter cloacae</i>	14 (12.4%)	14 (20%)	2 (4.4%)	0 (0%)	2 (13.3%)	32 (12.2%)
<i>Escherichia coli</i>	8 (7.1%)	1 (1.4%)	0 (0%)	4 (21.1%)	3 (20%)	16 (6.1%)
<i>Enterobacter aerogenes</i>	8 (7.1%)	1 (1.4%)	4 (8.9%)	1 (5.3%)	0 (0%)	14 (5.3%)
<i>Serratia marcescens</i>	3 (2.7%)	5 (7.1%)	1 (2.2%)	0 (0%)	0 (0%)	9 (3.4%)
<i>Citrobacter koseri</i>	3 (2.7%)	2 (2.9%)	1 (2.2%)	0 (0%)	0 (0%)	6 (2.3%)
<i>Enterobacter asburiae</i>	1 (0.9%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)	2 (0.8%)
<i>Klebsiella varicola</i>	1 (0.9%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)
<i>Citrobacter freundii</i>	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
<i>Citrobacter yougae</i>	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
<i>Morganella morganii</i>	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6.7%)	1 (0.4%)
<i>Pantoea dispersa</i>	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
<i>Proteus mirabilis</i>	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Non Fermentative Gram Negative bacilli	18 (15.9%)	14 (20%)	8 (17.8%)	0 (0%)	2 (13.3%)	42 (16%)
<i>Pseudomonas aeruginosa</i>	5 (4.4%)	9 (12.9%)	4 (8.9%)	0 (0%)	1 (6.7%)	19 (7.3%)
<i>Acinetobacter baumannii</i>	6 (5.3%)	4 (5.7%)	1 (2.2%)	0 (0%)	0 (0%)	11 (4.2%)
<i>Acinetobacter nosocomialis</i>	4 (3.5%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)	5 (1.9%)
<i>Aeromonas hydrophila</i>	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	1 (6.7%)	2 (0.8%)
<i>Stenotrophomonas maltophilia</i>	1 (0.9%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)
<i>Acinetobacter xylooxidans</i>	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
<i>Burkholderia cepacia</i>	1 (0.9%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)	2 (0.8%)
Candida Spp	6 (5.3%)	0 (0%)	2 (4.4%)	2 (10.5%)	0 (0%)	10 (3.8%)
<i>Candida spp</i>	6 (5.3%)	0 (0%)	2 (4.4%)	2 (10.5%)	0 (0%)	10 (3.8%)
Others	1 (0.9%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)
<i>Clostridium</i>	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
<i>Haemophilus Influenzae</i>	0 (0%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Total	113 (100%)	70 (100%)	45 (100%)	19 (100%)	15 (100%)	262 (100%)

8. Initial antibiotic therapy

In patients with ICU-BSI caused by a bacterial microorganism, initial antibiotic therapy was appropriate in 65.1% of cases. The appropriateness of initial antibiotherapy according to the responsible microorganism are reported in Figure 5.

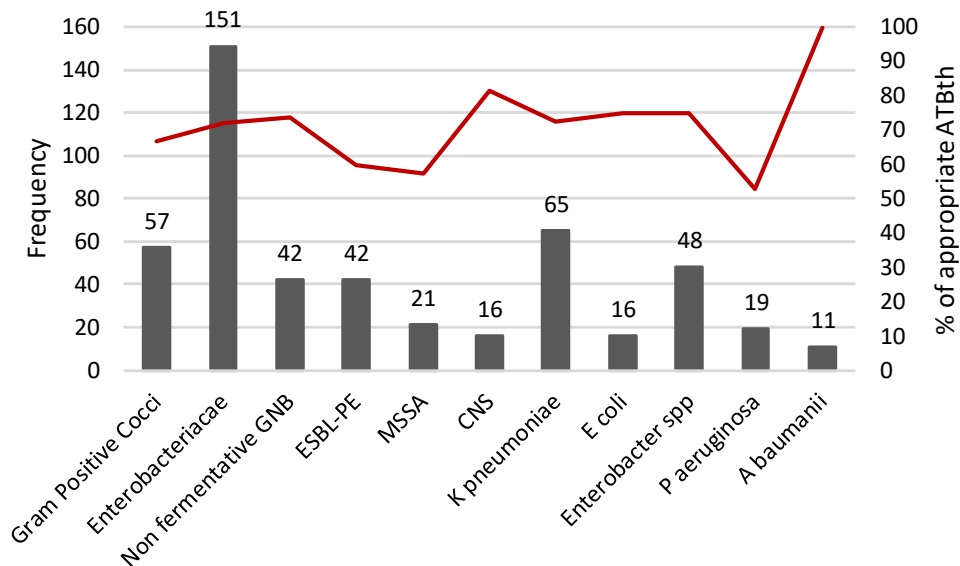


Figure 5: Appropriateness of initial antibiotherapy according to the responsible microorganism

9. ICU-BSI in ESBL-PE carriers

Epidemiological and clinical data of patients with ICU-BSI caused by ESBL and non ESBL-PE are reported in Appendix A. The causative microorganism of the first episode of ICU-BSI was ESBL-PE in 37 patients (16.6%). In patients with previous ESBL-PE carriage, the causative microorganism of the first episode of ICU-BSI was ESBL-PE in 29.8% of cases.

Variables associated to the occurrence of ICU-BSI caused by ESBL-PE and non ESBL-PE in univariate analysis are listed in Table XII.

Table XII: Variables associated to the occurrence of ICU-BSI caused by ESBL-PE and non ESBL-PE in univariate analysis

Variable	ICU-BSI caused by ESBL-PE		ICU-BSI caused by non ESBL-PE		p
	Nb	Result	Nb	Result	
Male gender	39	20 (51.3%)	184	130 (70.7%)	0.024
Traumatic	39	4 (10.3%)	184	64 (34.8%)	0.004
Origin	39		184		0.018
BMI	34	25 (24 - 34)	157	25 (22 - 29)	0.022
SAPS II	39	57 (42 - 75)	180	50 (39 - 63)	0.045
Cancer	39	4 (10.3%)	184	5 (2.7%)	0.022
Organ failure at admission	39	3 (2 - 4)	184	3 (2 - 3)	0.031
Hemodynamic	39	31 (79.5%)	184	112 (60.9%)	0.048
Respiratory	39	30 (76.9%)	184	116 (63%)	0.029
Liver	39	10 (25.6%)	184	18 (9.8%)	0.018
Active infection at admission	39	28 (71.8%)	184	89 (48.4%)	0.018
Antibiotics at admission	39	35 (89.7%)	184	119 (64.7%)	0.004
Aminoglycosides	39	10 (25.6%)	184	21 (11.4%)	0.012
Piperacillin-Tazobactam	39	13 (33.3%)	184	22 (12%)	0.000
Fluoroquinolones	39	9 (23.1%)	184	9 (4.9%)	0.000
Overall duration of AC	39	17 (13 - 26)	184	14 (9 - 21)	0.028
Multi-drug Resistant Bacteria carriage	39	38 (97.4%)	184	103 (56%)	0.000
ESBL-PE carriage	39	38 (97.4%)	184	83 (45.1%)	0.000
ESBL-PE carriage at admission	39	11 (28.2%)	184	17 (9.2%)	0.018
Non-fermenting organisms bacteremia	39	2 (5.1%)	184	40 (21.7%)	0.030
Enterobacteriaceae	39	39 (100%)	184	86 (46.7%)	0.000
ESBL-PE	39	39 (100%)	184	0 (0%)	0.000
Methicillin sensitive <i>staphylococcus aureus</i>	39	0 (0%)	184	22 (12%)	0.028
Carriage of ESBL-PE prior to ICU-BSI	39	26 (66.7%)	184	33 (17.9%)	0.000
Cefepime	39	4 (10.3%)	184	2 (1.1%)	0.001
Ciprofloxacin	39	2 (5.1%)	184	1 (0.5%)	0.019
Levofloxacin	39	6 (15.4%)	184	10 (5.4%)	0.020
Amikacin	39	14 (35.9%)	184	39 (21.2%)	0.028
3rd generation cephalosporins	39	14 (35.9%)	184	34 (18.5%)	0.008
Fluoroquinolones	39	8 (20.5%)	184	11 (6%)	0.002
Time from admission to ICU-BSI	39	12 (8 - 18.5)	184	8 (5 - 14)	0.018

In Multivariable analysis, factors independently associated with ESBL-PE as the causative microorganism of ICU-BSI were ESBL-PE carriage prior to ICU-BSI (OR: 7.273; 95%CI: 2.876-18.392; $p < 0.000$) and antibiotic exposure to fluoroquinolones (OR: 4.327; 95%CI: 1.120-16.728; $p = 0.034$).

10. Value of ESBL-PE carriage to predict ICU-BSI caused by ESBL-PE

In ESBL-PE carriers (prior to the ICU-BSI), 24 patients (40.7%) developed ICU-BSI caused by ESBL-PE. The sensitivity of ESBL-PE carriage to predict ESBL-PE as the causative microorganism of ICU-BSI was 64.9%. specificity was 81.2%. Positive Predictive Value was 40.7%. Negative Predictive Value was 92.1%. Q coefficient of Yule was 0.77 (high level range) and Youden index was 0.46. Predictive values of MDR-B carriage to predict ICU-BSI caused by the same organism are reported in Table XIII.

Table XIII : Predictive value of MDR-B carriage to predict ICU-BSI caused by the same organism

Facteur	Total	Nb ICU-BSI*	Ss	Sp	PPV	NPV	Q	Youden
MDRB carriage prior to ICU-BSI	69	45	0.67	0.79	0.44	0.9	0.76	0.45
ESBL carriage prior to ICU-BSI	57	37	0.65	0.81	0.41	0.92	0.77	0.46
ESBL-P- <i>E coli</i> carriage	18	1	1	0.92	0.06	1	1	0.92
ESBL-P- <i>K pneumoniae</i> carriage	64	29	0.9	0.8	0.41	0.98	0.95	0.7
ESBL-P- <i>Enterobacter Spp</i> carriage	27	10	0.3	0.89	0.11	0.96	0.54	0.19

* Nb of ICU-BSI caused by the same micro-organism

11. Outcome

Mortality rate in ICU was 25.6% in the general population. It was 21.5% in ESBL-PE carriers, 25% in ESBL-PE carriers with ICU-BSI caused by ESBL-PE vs 20% in ESBL-PE carriers with ICU-BSI caused by non ESBL-PE (p=ns).

Mortality at 28 days was 20.6% in the general population (Figure 6). It was 15.7% in ESBL-PE carriers with ICU-BSI. It was 19.4% in ESBL-PE carriers with ICU-BSI caused by ESBL-PE vs 14.1% in ESBL-PE carriers with ICU-BSI caused by non ESBL-PE (p=ns) (Figure 7). Epidemiological and clinical data of patients according to the 28-day mortality are reported in Appendix B.

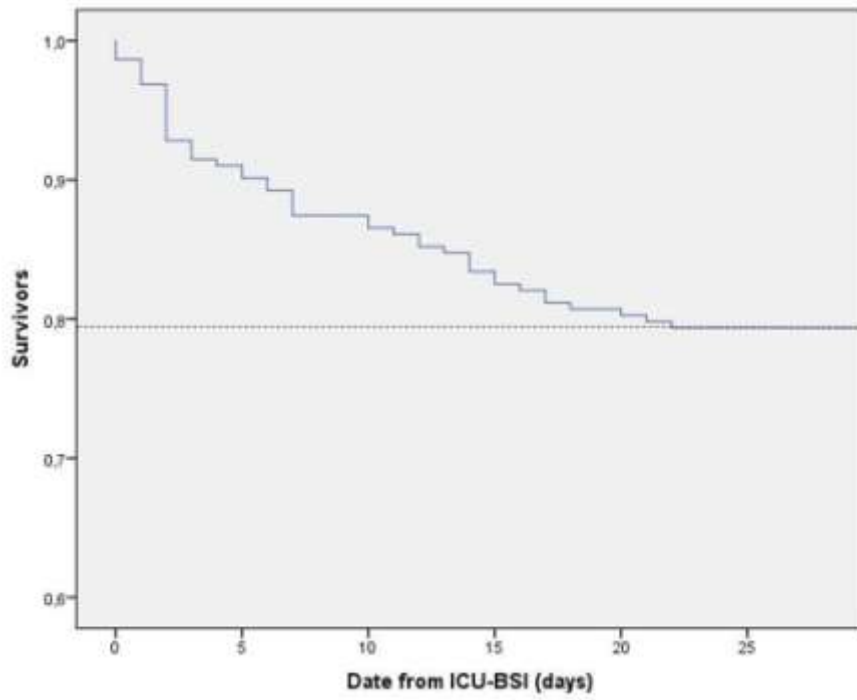


Figure 6: Mortality at day 28 in patients with ICU-BSI

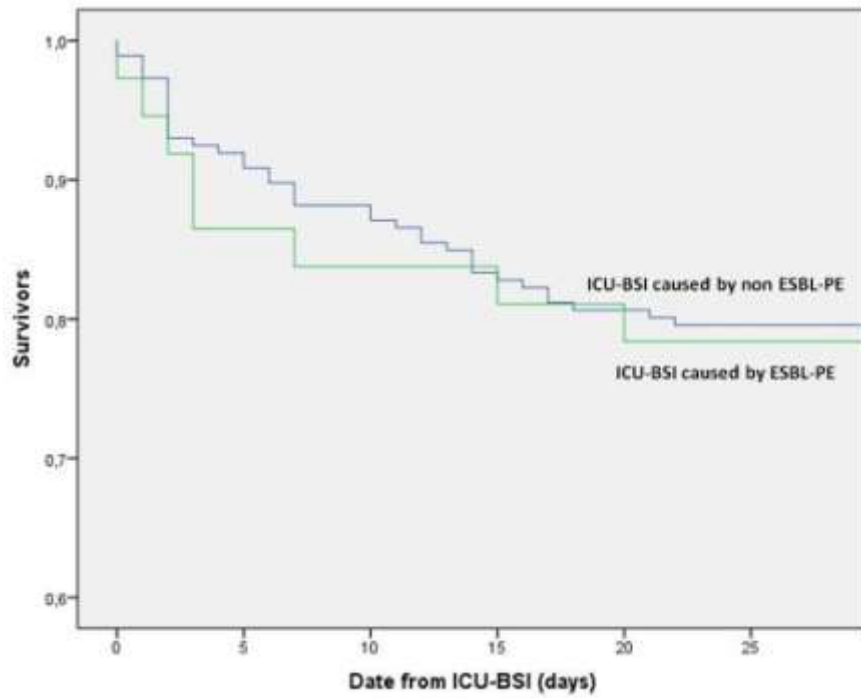


Figure 7: Mortality at day 28 in patients with ICU-BSI caused by ESBL-PE and non ESBL-PE (Log-Rank=ns)

The median ICU length of stay was 26 days (15-49). It was 35 days (20-61) days in ESBL-PE carriers. It was 38 days (20-60) in ESBL-PE carriers with ICU-BSI caused by ESBL-PE vs 35 days (21-64) in ESBL-PE carriers with ICU-BSI caused by non ESBL-PE (p=ns).

Variables associated to mortality at day 28 in univariate analysis are listed in Table XIV.

Table XIV: Variables associated to mortality at day 28 in univariate analysis

	Died at day 28		Alive at day 28		p
	Nb	Result	Nb	Result	
Age, years	46	54 (43 - 64)	177	47 (33 - 60)	0.026
Traumatic	46	6 (13%)	177	62 (35%)	0.004
SAPS	44	62 (46 - 76)	175	49 (39 - 61)	0.005
Immunodeficiency	46	12 (26.1%)	177	28 (15.8%)	0.049
Chronic renal failure	46	6 (13%)	177	5 (2.8%)	0.004
Hemodynamic failure at admission	46	36 (78.3%)	177	107 (60.5%)	0.025
Kidney failure at admission	46	22 (47.8%)	177	52 (29.4%)	0.018
Duration of MV, days	44	14.5 (11 - 24)	163	23 (14 - 39)	0.008
Tracheostomy	44	1 (2.3%)	163	36 (22.1%)	0.002
Renal replacement therapy	46	16 (34.8%)	177	27 (15.3%)	0.003
Amoxicillin clavulanate at admission	46	8 (17.4%)	177	62 (35%)	0.022
ATB exposure during hospitalization	46	39 (84.8%)	177	167 (94.4%)	0.029
Overall duration of CVC	46	16 (10 - 28)	177	21 (13 - 41)	0.023
Duration of CVC without infection	11	9 (7 - 16)	39	18 (13 - 29)	0.044
Overall duration of AC	46	13 (8 - 19)	177	16 (10 - 23)	0.042
Multi-drug Resistant Bacteria carriage	46	23 (50%)	177	118 (66.7%)	0.037
ESBL-PE carriage	46	19 (41.3%)	177	102 (57.6%)	0.048
ICU-BSI caused by one organism	46	43 (93.5%)	177	141 (79.7%)	0.028
Septic shock	46	19 (41.3%)	177	27 (15.3%)	0.000
ICU LOS (days)	46	17 (11 - 24)	177	32 (17 - 58)	0.002

In Multivariable analysis, factors independently associated with mortality at day 28 from the occurrence of ICU-BSI were traumatic category at admission (OR: 0.346; 95%CI: 0.134-0.894; p=0.028) and septic shock associated to ICU-BSI (OR: 3.317; 95%CI: 1.561-7.050; p=0.002) (Figure 8).

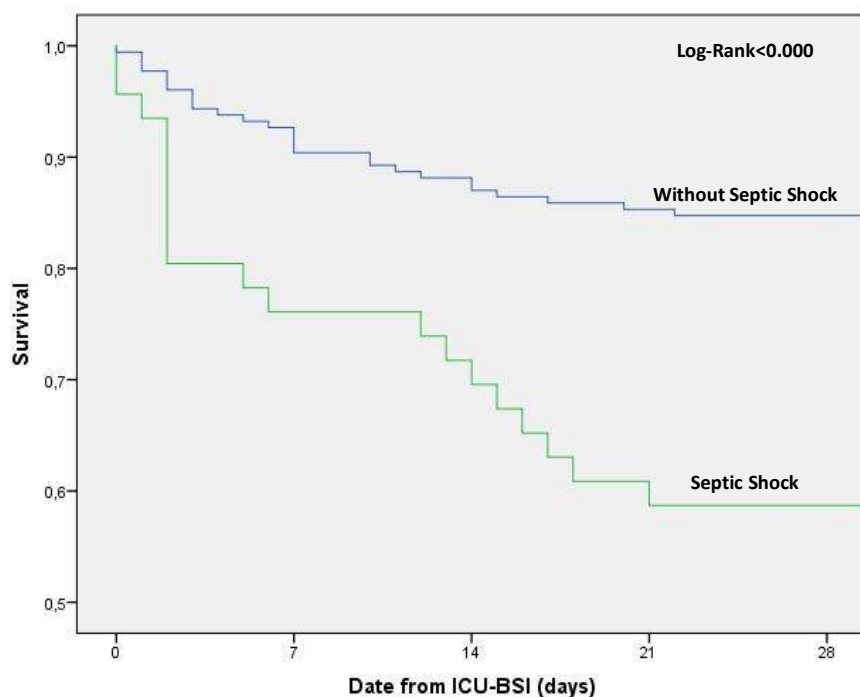


Figure 8: Mortality at day 28 in patients with ICU-BSI with and without associated septic shock (Log-Rank<0.0001)

The analysis of the mortality at day 28 according to the causative organism and in comparison to the mortality recorded in case of ICU-BSI caused by methicillin susceptible *Staphylococcus aureus* showed no statistically difference between organisms (Table XV and Figure 9)

Table XV: The mortality at day 28 according to the causative organism

Organism	Mortality (%)	OR	Min	Max	p
Methicillin susceptible <i>S aureus</i>	18.2	reference			
Enterobacteriaceae	17.3	0.255	0.341	4.614	0.732
<i>Klebsiella pneumoniae</i>	9.2	0.245	0.114	1.772	0.245
<i>Enterobacter spp</i>	14.9	0.788	0.204	3.033	0.728
<i>Escherichia coli</i>	37.5	2.700	0.613	11.892	0.182
ESBL-PE	21.6	1.241	0.326	4.725	0.751
Non Fermentative Gram Negative bacilli	12.2	0.644	0.153	2.715	0.447
<i>Pseudomonas aeruginosa</i>	10.5	0.529	0.086	3.275	0.489
<i>Acinetobacter baumannii</i>	9.1	0.450	0.044	4.596	0.492
<i>Candida spp</i>	40.0	3.000	0.567	15.867	0.186
<i>Coagulase-negative staphylococci</i>	33.3	2.250	0.490	10.341	0.292

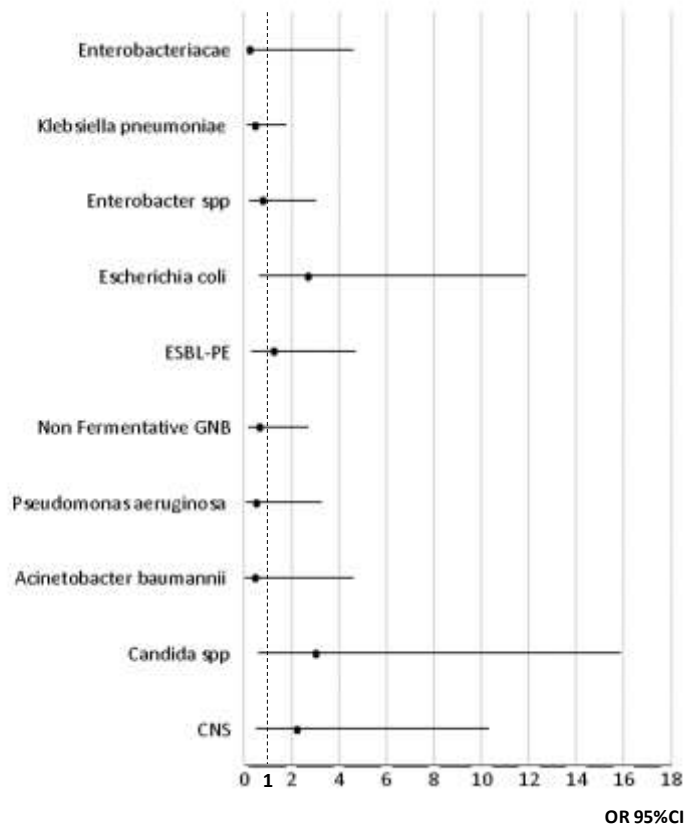


Figure 9: The mortality at day 28 according to the causative organism

Discussion

1. Epidemiology

ICU-acquired BSI complicated 2 to 7 %of admissions, with an incidence rate ranging between 4and 9per 1000 patient days at risk[2,4,5,32].The median time to acquired BSI in ICU is 7-18 days from admission[4,15]. It depend on the causative bacteria with 13 days for *E coli*, 37 days for *K pneumoniae* and 11 days for *P mirabilis*[2,18].

Prowle et al. [4] in a retrospective study of 6339 ICU admissions, 330 of whom were complicated by BSI (5.2%). Median time to the first positive culture was 7 days (IQR 5-12).

In our study, ICU-BSI complicated 9.5% of admissions giving a density incidence of 10.3 ICU-BSI/1000 days of hospitalization. This rate is higher than the one reported in the litterature. In addition, we found a high variability over the 78 months of the study. The median time to the first positive blood culture was 9 days (IQR 5-16). This delay is similar to that reported by Prowle et al. [4].

2. The source of ICU-BSI

BSIs may be the consequence of the bloodstream diffusion of microorganisms from a localized infection (secondary BSI) or may be the only identifiable infectious process (primary BSI) [33]. The rate of unknown source or primary BSI is the most frequent, with 23 to 33.5% [2,15,34,35]. For secondary ICU-BSI, the major reported causes are catheter-related (CR-BSIs) in most of studies (21 to 30%), followed by lung infection or Ventilator-Associated-Pneumonia (15 to 21%), biliary and urinary tracks (14 to 45%), followed by surgical wound, peritonitis or soft tissue infection [2,15,34,35].

In our study, we found a high level of primary ICU-BSI (44%). For secondary ICU-BSI, the major causes were VAP (25,6%) and catheter related infection (17,5%). These rates are concordant with those reported in the literature. A deeper analysis of the characteristics of primary ICU-BSI is needed to allow preventive measures.

3. Risk factors of acquired BSI

Patients acquiring BSI are significantly sicker at ICU admission and had more co-morbidities. In addition, they need mechanical ventilation, renal replacement therapy, and invasive techniques, making them at greater risk to develop health care associated infection [4,36–

39].Indeed, the intravascular catheters use is recognized as the most important factor contributing to the occurrence of ICU-BSI [40,41].

In our study, patients were exposed to mechanical ventilation in 92.8% of cases, to venous catheterization in 96.5%, to arterial catheterization in 92.4% and to renal replacement therapy in 19.3% of cases. Those high exposure rates are explained by the severity of our patients and makes them at high risk to develop health care associated infection mainly ICU-BSI. The severity of our patients was measured at admission by the SAPS II and SOFA scores.

4. Microbiology

In the EUROBACT study (1,156 ICU patient's), 57.6% of microorganisms responsible of ICU-BSI were Gram-negative, 33.4% were Gram-positive and 1.2 % of ICU-BSI were due to strict anaerobes [15]. *Candida* spp can be responsible of 8-15% of cases of ICU-BSI [4,15].

Prowle et al. [4] in a retrospective study of 330 ICU-BSI found that the main causative microorganisms were Gram negative Bacilli (28.2%), *Staphylococcus aureus* (26.7%), Coagulase-negative staphylococci (24.3%), Enterococci (17.0%), and *Candida* species (15.5%).

Corona et al. [42] conducted a prospective observational non interventional study in 132 ICUs from 26 countries. They analyzed 1697 episodes of BSI. Among them, 915 (53.9%) were acquired in ICU. The main causative microorganisms were Gram negative Bacilli (37.3%), Coagulase-negative staphylococci (29.6%), *S aureus* (23.6%), Enterococci (11.4%), and *Candida species* (6.5%).

Candida spp plays a major role in ICU, accounting for 6 to 15% of cases of BSIs[15,43] with a prevalence of 6.9 per 1000 patients [1], and a predominance of primary source of infection [2]. In a fungemia sub group of EUROBACT study, *Candida albicans* was the most frequent fungus isolated (57.1%), followed by *Candida glabrata* (15.3%) and *Candida parapsilosis* (10.2%) [43].

In our study, ICU-BSI was caused by one microorganism in 184 cases (82%) and two microorganisms in 39 cases (17.5%). The microorganism recovered was an Enterobacteriaceae in 151 patients (68 %) and a Gram-positive cocci in 26 % of patients. It was ESBL producer in 37 cases (24.5%). *Candida spp* was recovered in 10 cases (4.9%). In two cases there was coinfection with *Candida spp.* and *K pneumoniae*. The causative

microorganism of the first episode of ICU-BSI was ESBL-PE in 37 patients (16.6%). In patients with previous ESBL-PE carriage, the causative microorganism of the first episode of ICU-BSI was ESBL-PE in 29.8% of cases. In Multivariable analysis, factors independently associated with ESBL-PE as the causative microorganism of ICU-BSI were ESBL-PE carriage prior to ICU-BSI (OR: 7.273; 95%CI: 2.876-18.392; $p < 0.000$) and antibiotic exposure to fluoroquinolones (OR: 4.327; 95%CI: 1.120-16.728; $p = 0.034$). These results are important to identify patients with suspected ESBL-PE in case of ICU-BSI and to guide initial empiric antibiotic therapy.

5. Prognosis

Patients with ICU-BSI have a longer ICU or hospital stay, than those without ICU-BSI (median 15 days vs. 5 days; $P < 0.001$) [2,4]. In addition, ICU-BSI is independently associated to a higher mortality rate [2,5,7,15,44]. This higher mortality was not influenced by the timing of acquisition of ICU-BSI [15].

Prowle et al. [4] in a retrospective study of 330 ICU-BSI in 6339 ICU admissions (5.2%) found that the overall mortality was 23.5% (41.2% in patients with BSI and 22.5% in those without). Patients who developed ICU-BSI had higher illness severity at ICU admission (median APACHE III score: 79 vs. 68, $P < 0.001$). After controlling for illness severity and baseline demographics, ICU-BSI remained independently associated with risk of death (hazard ratio from diagnosis 2.89; 95% confidence interval 2.41-3.46; $P < 0.001$). However, only 5% of the deaths in this model could be attributed to ICU-BSI, equivalent to an absolute decrease in survival of 1% of the total population. When analyzed by microbiological classification, *Candida*, *Staphylococcus aureus* and gram-negative bacilli infections were independently associated with increased risk of death. In a sub-group analysis intravascular catheter associated BSI remained associated with significant risk of death (hazard ratio 2.64; 95% confidence interval 1.44-4.83; $P = 0.002$).

In addition, source control of ICU-BSI is shown to be independently related to outcome [7]. Some sources are associated with a higher fatality rate like respiratory [45], unknown [2], or abdominal sources [5,15]. On the opposite, some authors found that BSI due to catheter-related infection did not increase the risk of death [2].

In an other hand, some author suggest that the virulence of the microorganism rather than the source of infection may be more important in determining outcome, and that prevention of

these infections (predominantly *S aureus*, Gram negative bacilli and *Candida*) is an important therapeutic goal [4]. Indeed, compared with *S aureus* and adjusted by age, sex and type of ICU, *S maltophilia* was associated with significantly higher ICU mortality (OR 1.71) as followed by Enterococci (OR 1.20), *Ecoli* (OR 1.24), *C albicans* (OR 1.37), non albicans *Candida spp.* (OR 1.49) and *P aeruginosa* (OR 1.49) [46].

Other factors are reported to be associated to 28 day mortality like older patients, chronic respiratory disease or immune deficiency, septic shock or higher SOFA score or cardiac diseases, organ dysfunction within two days before ICU-BSI, transfer from another ward, nutrition, intravenous or urinary tract catheters within a week before and or do-not-resuscitation order [2,15].

In our study, Mortality at 28 days was 20.6% in the general population and 15.7% in patients with ESBL-PE carriage. It was 19.4% in ESBL-PE carriers with ICU-BSI caused by ESBL-PE vs 14.1% in ESBL-PE carriers with ICU-BSI caused by non ESBL-PE. The difference did not reach the level of significance. The analysis of the impact of causative microorganism of ICU-BSI compared to *S aureus* on 28-day mortality, showed no difference between organisms.

In Multivariable analysis, factors independently associated with mortality at day 28 from the occurrence of ICU-BSI were traumatic category of admission (OR: 0.346; 95%CI: 0.134-0.894; p=0.028) and septic shock associated to ICU-BSI (OR: 3.317; 95%CI: 1.561-7.050; p=0.002). Indeed, septic shock is a severe condition associated to a high mortality rate reaching 40% in some cases [27]. Regarding patients with traumatic category at admission, they are typically younger and in good condition of health making them at lower risk of mortality in ICU.

6. Appropriate empirical ATB therapy

A prompt initiation of an effective antibiotic treatment should be tailored in each single patient on the basis of the infection source, the most frequent isolated pathogens and the risk of antibiotic resistances[1]. In case of ICU-BSI, the impact of early appropriate antibiotic therapy on outcome is controversial. Kumar et al. [47] found that in adequate therapy within 6h after onset of hypotension was associated with more than nine-fold increase in the risk of death in patients with septic shock and documented BSI. However, Valles et al. [37]found that appropriate antibiotic therapy (given in the 24 h after the blood sample test result

availability) had no influence on mortality. Corona et al. [42] investigated the delay from the first positive blood culture sampling to the first day of effective antibiotic therapy against the microorganisms isolated. The adjusted ORs for death were 1.34, 1.75, and 0.97 at 1, 2, and 3 days respectively (non significant), indicating an absence of effect on mortality. Similar results were obtained in the EUROBACT study [49] where a very early treatment (<1 day after the first positive blood culture taken) was not associated with a decrease in the risk of death as compared with less than 2 days and less than 5 days. One of the limitations to compare these results is that the definition of adequate or appropriate antimicrobial therapy in ICU patients varies between studies [37,42,48].

In our study, analysis of patients with ICU-BSI caused by a bacterial microorganism (215 patients) showed an appropriateness level of initial antibiotic therapy at 65.1%. The comparison of patients with and without appropriate initial antibiotic therapy did not find any difference in the outcome. This result is similar to others reported in the literature but should be interpreted with caution because we did not monitor the severity of patients at the day of the diagnosis of ICU-BSI. For this, we think that any analysis without adjustment on the severity at the moment of the diagnosis of ICU-BSI is hazardous.

Despite the abundant literature, the effect of ICU-BSI on mortality and length of stay is still uncertain[50].Part of the variation in estimates can be explained by differences in case-mix, quality of care and antimicrobial resistance rates. However, there are also several methodological issues, which can impact estimates and are often overlooked. The fact that ICU-BSI have a time-dependent nature has often been ignored. Indeed, time-modified confounding occurs when the causal relation between a time-fixed or time-varying confounder and the treatment or outcome changes over time.

Clinician, have to find the balance between providing an early adequate empiric coverage and a rational use of broad-spectrum antimicrobials. Indeed, to focus on the only goal of providing a broad-spectrum antibiotic can be a driver for over use of antimicrobials which is the main reason for the increasing selection of resistances.

7. Limits of the study

Our study has several limitations. First, it is a retrospective monocentric work. Second, the sample size is not large enough to adjust for confounding variables. In addition, we did not

studied some time-dependent variables like severity of illness at the day of the diagnosis of ICU-BSI.

Conclusion

ICU-BSI complicates 9.5% of admissions in our center giving a density incidence of 10.3 ICU-BSI/1000 days. The predominant primitive origin (44%) matched well with literature. The ICU-BSI from an identified origin were dominated by VAP (25,6%) and catheter-associated infection (17,5%).

The isolated microorganisms were dominated by *Enterobacteriae* (68%) and an ESBL-PE was isolated in 24% of cases. Factors significantly associated to ICU-BSI caused by ESBL-PE, were ESBL-PE carrying (OR 7,2) and antibiotic exposure to fluoroquinolones (OR 4,3) prior to ICU-BSI. The mortality remains elevated with 25% in the total population, and associated prognosis factors were non traumatic category at admission and septic shock the day of the ICU-BSI. Further studies with deeper analysis and adjustment on confounder variables are needed to search for pertinent associated factors to the outcome of ICU-BSI allowing rapid detection of at risk patients and targeted preventive measures.

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Appendix A: Epidemiological and clinical parameters and outcome of patients with USI-BSI caused by ESBL-PE and non ESBL-PE

Appendix A (part 1) Parameter	ICU-BSI caused by BLSE-PE		ICU-BSI caused by non BLSE-PE		p
	Nb	Result	Nb	Result	
Age, years	39	46 (32 - 67)	184	49 (36 - 60)	0.620
Male gender	39	20 (51.3%)	184	130 (70.7%)	0.024
BMI	34	25 (24 - 34)	157	25 (22 - 29)	0.022
SAPS II	39	57 (42 - 75)	180	50 (39 - 63)	0.045
Type of admission					
Traumatic	39	4 (10.3%)	184	64 (34.8%)	0.004
Medical past	39	25 (64.1%)	184	104 (56.5%)	0.589
Arterial hypertension	39	11 (28.2%)	184	60 (32.6%)	0.763
Diabetes mellitus	39	7 (17.9%)	184	22 (12%)	0.242
Cancer	39	4 (10.3%)	184	5 (2.7%)	0.022
Immunodeficiency	39	13 (33.3%)	184	27 (14.7%)	0.336
Chronic renal failure	39	3 (7.7%)	184	8 (4.3%)	0.329
Chronic respiratory failure	39	1 (2.6%)	184	3 (1.6%)	0.648
Sickle cell disease	39	4 (10.3%)	184	6 (3.3%)	0.244
Organ failure at admission					
Hemodynamic	39	31 (79.5%)	184	112 (60.9%)	0.048
Respiratory	39	30 (76.9%)	184	116 (63%)	0.029
Neurologic	39	26 (66.7%)	184	123 (66.8%)	0.915
Kidney	39	17 (43.6%)	184	57 (31%)	0.071
Liver	39	10 (25.6%)	184	18 (9.8%)	0.018
Hematologic	39	12 (30.8%)	184	37 (20.1%)	0.092
Mechanical ventilation	39	37 (94.9%)	184	170 (92.4%)	0.648
Time from admission to MV	37	0 (0 - 0)	170	0 (0 - 0)	0.908
Duration of MV. days	37	26 (14 - 42)	170	20 (12 - 31)	0.339
Ventilator Associated Pneumoniae	37	14 (37.8%)	170	83 (48.8%)	0.372
Duration of MV without VAP. days	14	11 (8 - 17)	83	7 (4 - 14)	0.595
Tracheostomy	37	5 (13.5%)	170	32 (18.8%)	0.543
Time from admission to tracheostomy	5	33 (33 - 40)	33	29 (23 - 42)	0.912
Unscheduled detubation	37	1 (2.7%)	170	6 (3.5%)	0.851
Renal replacement therapy	39	10 (25.6%)	184	33 (17.9%)	0.191
Time from admission to RRT	10	1 (0 - 3)	33	2 (0 - 8)	0.437
Active infection at admission					
Bacteraemia at admission	28	7 (25%)	89	16 (18%)	0.950
Antibiotics at admission					
Amoxicillin clavulanate	39	9 (23.1%)	184	61 (33.2%)	0.311
Aminoglycosides	39	10 (25.6%)	184	21 (11.4%)	0.012
Piperacillin-Tazobactam	39	13 (33.3%)	184	22 (12%)	0.000
3rd generation cephalosporins	39	8 (20.5%)	184	26 (14.1%)	0.238
Imipenem	39	3 (7.7%)	184	7 (3.8%)	0.767
Fluoroquinolones	39	9 (23.1%)	184	9 (4.9%)	0.000

Appendix A (part 2) Parameter	ICU-BSI caused by BLSE-PE		ICU-BSI caused by non BLSE-PE		p
	Nb	Result	Nb	Result	
Metronidazole	39	1 (2.6%)	184	2 (1.1%)	0.433
Central venous catheter	39	38 (97.4%)	184	178 (96.7%)	0.868
CVC related Infection	39	12 (30.8%)	184	38 (20.7%)	0.110
Overall duration of CVC	39	27 (15 - 47)	184	19 (11 - 32)	0.076
Duration of CVC without infection	12	21 (11 - 29)	38	16 (9 - 26)	0.822
Arterial catheter	39	37 (94.9%)	184	169 (91.8%)	0.217
Arterial catheter related Infection	39	4 (10.3%)	184	29 (15.8%)	0.455
Overall duration of AC	39	17 (13 - 26)	184	14 (9 - 21)	0.028
Duration of AC without infection	3	14 (14 - 19)	26	9 (8 - 15)	0.330
Multi-drug Resistant Bacteria carriage	39	38 (97.4%)	184	103 (56%)	0.000
ESBL-PE carriage	39	38 (97.4%)	184	83 (45.1%)	0.000
ESBL-PE carriage at admission	39	11 (28.2%)	184	17 (9.2%)	0.018
ICU-BSI microbiology	39		184		0.492
ICU-BSI caused by one organism	39	34 (87.2%)	184	151 (82.1%)	0.802
Non-fermenting organism	39	2 (5.1%)	184	40 (21.7%)	0.030
Enterobacteriaceae	39	39 (100%)	184	86 (46.7%)	0.000
ESBL-PE	39	39 (100%)	184	0 (0%)	0.000
Candida Spp	39	0 (0%)	184	10 (5.4%)	0.129
Methicillin sensitive <i>Staphylococcus aureus</i>	39	0 (0%)	184	22 (12%)	0.028
Coagulase negative staphylococcus	39	0 (0%)	184	13 (7.1%)	0.074
Septic shock	39	9 (23.1%)	184	37 (20.1%)	0.882
Appropriate ATBth within 24h	39	24 (61.5%)	184	127 (69%)	
ESBL-PE carriage prior to ICU-BSI	39	26 (66.7%)	184	33 (17.9%)	0.000
ATB exposure prior to ICU-BSI					
Amoxicillin clavulanate	39	8 (20.5%)	184	57 (31%)	0.270
Aminoglycosides	39	17 (43.6%)	184	56 (30.4%)	0.061
Piperacillin-Tazobactam	39	12 (30.8%)	184	44 (23.9%)	0.261
3rd generation cephalosporins	39	14 (35.9%)	184	34 (18.5%)	0.008
Imipenem	39	6 (15.4%)	184	18 (9.8%)	0.554
Fluoroquinolones	39	8 (20.5%)	184	11 (6%)	0.002
Metronidazole	39	1 (2.6%)	184	5 (2.7%)	0.996
Outcome	0		0		
ICU LOS, days	39	37 (18 - 57)	184	24 (15 - 48)	0.731
Length of stay greater than 48 hours	39	39 (100%)	184	183 (99.5%)	0.655
Time from admission to BSI	39	12 (8 - 18.5)	184	8 (5 - 14)	0.018
Delay between ICU-BSI and ICU discharge	39	20 (8 - 35)	184	14 (6 - 35)	0.953
Death	39	12 (30.8%)	184	45 (24.5%)	0.823
28-day mortality	39	10 (25.6%)	184	36 (19.6%)	0.870

Appendix B: Epidemiological and clinical parameters of patients with USI-BSI according to the 28-day mortality

Appendix B (Part 1) Parameter	Dead at 28 day		Alive at 28 day		P
	Nb	Result	Nb	Result	
Age, years	46	54 (43 - 64)	177	47 (33 - 60)	0.026
Male gender	46	31 (67.4%)	177	119 (67.2%)	0.984
BMI	40	24 (21 - 31)	151	25 (22 - 30)	0.398
SAPS II	44	62 (46 - 76)	175	49 (39 - 61)	0.005
Type of admission					
Traumatic	46	6 (13%)	177	62 (35%)	0.004
Medical past					
Arterial hypertension	46	18 (39.1%)	177	53 (29.9%)	0.223
Diabetes mellitus	46	7 (15.2%)	177	22 (12.4%)	0.616
Cancer	46	0 (0%)	177	9 (5.1%)	0.118
Immunodeficiency	46	12 (26.1%)	177	28 (15.8%)	0.049
Chronic renal failure	46	6 (13%)	177	5 (2.8%)	0.004
Chronic respiratory failure	46	1 (2.2%)	177	3 (1.7%)	0.827
Sickle cell disease	46	2 (4.3%)	177	8 (4.5%)	0.960
Organ failure at admission					
Hemodynamic	46	36 (78.3%)	177	107 (60.5%)	0.025
Respiratory	46	33 (71.7%)	177	113 (63.8%)	0.316
Neurologic	46	31 (67.4%)	177	118 (66.7%)	0.926
Kidney	46	22 (47.8%)	177	52 (29.4%)	0.018
Liver	46	8 (17.4%)	177	20 (11.3%)	0.267
Hematologic	46	13 (28.3%)	177	36 (20.3%)	0.248
Mechanical ventilation	46	44 (95.7%)	177	163 (92.1%)	0.404
Time from admission to MV					
Time from admission to MV	44	0 (0 - 0)	163	0 (0 - 0)	0.193
Duration of MV, days	44	14.5 (11 - 24)	163	23 (14 - 39)	0.008
Ventilator Associated Pneumoniae	44	16 (36.4%)	163	81 (49.7%)	0.116
Duration of MV without VAP, days	16	8 (4 - 14)	81	7 (5 - 16)	0.465
Tracheostomy	44	1 (2.3%)	163	36 (22.1%)	0.002
Time from admission to tracheostomy	1	19 (19 - 19)	37	30 (24 - 40)	0.336
Unscheduled detubation	44	2 (4.5%)	163	5 (3.1%)	0.630
Renal replacement therapy					
Renal replacement therapy	46	16 (34.8%)	177	27 (15.3%)	0.003
Time from admission to RRT	16	2 (0 - 9)	27	1 (0 - 4)	0.271
Active infection at admission					
BSI at admission	46	24 (52.2%)	177	93 (52.5%)	0.964
Antibiotics at admission					
Amoxicillin clavulanate	46	8 (17.4%)	177	62 (35%)	0.022
Aminoglycosides	46	7 (15.2%)	177	24 (13.6%)	0.772
Piperacillin-Tazobactam	46	9 (19.6%)	177	26 (14.7%)	0.418
3rd generation cephalosporins	46	6 (13%)	177	28 (15.8%)	0.641
Imipenem	46	3 (6.5%)	177	7 (4%)	0.454
Fluoroquinolones	46	2 (4.3%)	177	16 (9%)	0.298
Metronidazole	46	0 (0%)	177	3 (1.7%)	0.374

Appendix B (Part 2) Parameter	Dead at 28 day		Alive at 28 day		P
	Nb	Result	Nb	Result	
Central venous catheter	46	45 (97.8%)	177	171 (96.6%)	0.673
CVC related Infection	46	11 (23.9%)	177	39 (22%)	0.785
Overall duration of CVC	46	16 (10 - 28)	177	21 (13 - 41)	0.023
Duration of CVC without infection	11	9 (7 - 16)	39	18 (13 - 29)	0.044
Arterial catheter	46	42 (91.3%)	177	164 (92.7%)	0.758
Arterial catheter related Infection	46	5 (10.9%)	177	28 (15.8%)	0.400
Overall duration of AC	46	13 (8 - 19)	177	16 (10 - 23)	0.042
Duration of AC without infection	4	9 (8 - 10)	25	12 (8 - 18)	0.367
Multi-drug Resistant Bacteria carriage	46	23 (50%)	177	118 (66.7%)	0.037
ESBL-PE carriage	46	19 (41.3%)	177	102 (57.6%)	0.048
ESBL-PE carriage at admission	46	7 (15.2%)	177	21 (11.9%)	0.541
ICU-BSI microbiology	46		177		0.396
ICU-BSI caused by one organism	46	43 (93.5%)	177	141 (79.7%)	0.028
Non-fermenting organism	46	6 (13%)	177	34 (19.2%)	0.332
Enterobacteriaceae	46	22 (47.8%)	177	111 (62.7%)	0.067
ESBL-PE	46	8 (17.4%)	177	29 (16.4%)	0.870
Candida Spp	46	4 (8.7%)	177	7 (4%)	0.186
Methicillin sensitive <i>Staphylococcus aureus</i>	46	4 (8.7%)	177	18 (10.2%)	0.765
Coagulase negative staphylococcus	46	5 (10.9%)	177	10 (5.6%)	0.208
Septic shock	46	19 (41.3%)	177	27 (15.3%)	0.000
Appropriate ATBth within 24h	46	30 (65.2%)	177	121 (68.4%)	0.685
ESBL-PE carriage prior to ICU-BSI	46	14 (30.4%)	177	45 (25.4%)	0.492
ATB exposure prior to ICU-BSI	46	29 (63%)	177	130 (73.4%)	0.165
Amoxicillin clavulanate	46	9 (19.6%)	177	56 (31.6%)	0.108
Aminoglycosides	46	13 (28.3%)	177	60 (33.9%)	0.468
Piperacillin-Tazobactam	46	8 (17.4%)	177	48 (27.1%)	0.175
3rd generation cephalosporins	46	7 (15.2%)	177	41 (23.2%)	0.243
Imipenem	46	7 (15.2%)	177	17 (9.6%)	0.274
Fluoroquinolones	46	3 (6.5%)	177	16 (9%)	0.586
Metronidazole	46	1 (2.2%)	177	5 (2.8%)	0.808
Outcome	0		0		
ICU LOS, days	46	17 (11 - 24)	177	32 (17 - 58)	0.002
Length of stay greater than 48 hours	46	46 (100%)	177	176 (99.4%)	0.609
Time from admission to BSI	46	8 (5 - 16)	177	9 (5 - 15)	0.607
Delay between ICU-BSI and ICU discharge	46	6 (2 - 14)	177	19 (8 - 39)	0.002
Death	46	46 (100%)	177	11 (6.2%)	0.000

SERMENT D'HIPPOCRATE

Au moment d'être admis à exercer la médecine, en présence des maîtres de cette école et de mes condisciples, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité qui la régissent.

Mon premier souci sera, de rétablir, de préserver ou de promouvoir la santé dans tous les éléments physiques et mentaux, individuels collectifs et sociaux. Je respecterai toutes les personnes, leur autonomie et leur volonté, sans aucune discrimination selon leur état ou leurs convictions.

J'interviendrai pour les protéger si elles sont affaiblies, vulnérables ou menacées dans leur intégrité ou dignité.

Même sous la contrainte, je ne ferai usage de mes connaissances contre les lois de l'humanité.

J'informerai les patients de décisions envisagées, de leurs raisons et de leurs conséquences.

Je ne tromperai jamais leur confiance et n'exploiterai pas le pouvoir hérité des circonstances pour forcer leurs consciences.

Je donnerai mes soins à l'indigent et à quiconque me les demandera.

Je ne me laisserai influencer ni par la recherche du gain ni par la recherche de la gloire.

Admis dans l'intimité des personnes, je tairai les secrets qui me sont confiés. Reçu à l'intérieur des maisons, je respecterai les secrets des foyers.

Et ma conduite ne servira pas à corrompre les mœurs.

Je ferai tout pour soulager les souffrances, sans acharnement.

Je ne provoquerai jamais la mort délibérément.

Je préserverai l'indépendance nécessaire à l'accomplissement de ma mission.

Que je sois modéré en tout, mais insatiable de mon amour de la science.

Je n'entreprendrai rien qui ne dépasse mes compétences ; je les entretiendrai et les perfectionnerai pour assurer au mieux les services qui me seront demandés.

J'apporterai mon aide à mes confrères ainsi qu'à leurs familles dans l'adversité.

Que les hommes et mes confrères m'accordent leur estime si je suis fidèle à mes promesses,

Que je sois déshonoré et méprisé si j'y manque.