UNIVERSITE DES ANTILLES
ET DE LA GUYANE
2019

FACULTE DE MEDECINE
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

Examinateurs de la thèse :

M Professeur DJOSSOU Félix Président

M Professeur COUPIE Pierre.

M Professeur CARLES Michel

M Professeur DEMAR Magalie

M Dr HOMMEL Didier

M Dr KALLEL Hatem Docteur en Médecine directeur de thèse

UNIVERSITE DES ANTILLES

****

****

FACULTE DE MEDECINE HYACINTHE BASTARAUD

***

Liste des enseignants 2018/2019

Président de l'Université : Eustase JANKY

Doyen de la Faculté de Médecine : Raymond CESAIRE

Vice-Doyen de la Faculté de Médecine : Suzy DUFLO

NEVIERE Rémi — **Physiologie**
CHU de MARTINIQUE
Tel : 0696 19 44 99

Pascal BLANCHET — **Chirurgie Urologique**
CHU de POINTE- À -PITRE/ABYMES
Tel : 05 90 89 13 95 - Tel/Fax 05 90 89 17 87

André-Pierre UZEL — **Chirurgie Orthopédique et Traumatologie**
CHU de POINTE-A-PITRE/ABYMES
Tel : 05 90 89 14 66 – Fax : 0590 89 17 44

Pierre COUPPIE — **Dermatologie**
CH de CAYENNE
Tel : 05 94 39 53 39 - Fax : 05 94 39 52 83

Thierry DAVID — **Ophtalmologie**
CHU de POINTE-A-PITRE/ABYMES
Tel : 05 90 89 14 55 - Fax : 05 90 89 14 51

Suzy DUFLO — **ORL – Chirurgie Cervico-Faciale**
CHU de POINTE-A-PITRE/ABYMES
Tel : 05 90 93 46 16

EustaseJANKY — **Gynécologie-Obstétrique**
CHU de POINTE-A-PITRE/ABYMES

Tel 05 90 89 13 89 - Fax 05 90 89 13 88

DE BANDT Michel — **Rhumatologie**
CHU de MARTINIQUE
Tel : 05 96 55 23 52 - Fax : 05 96 75 84 44

François ROQUES — **Chirurgie Thoracique et Cardiovasculaire**
CHU de MARTINIQUE
Tel : 05 96 55 22 71 - Fax : 05 96 75 84 38

Jean ROUDIE — **Chirurgie Digestive**
CHU de MARTINIQUE
Tel : 05 96 55 21 01
Tel : 05 96 55 22 71 - Fax : 05 96 75 84 38

Jean-Louis ROUVILLAIN — **ChirurgieOrthopédique**
CHU de MARTINIQUE
Tel : 05 96 55 22 28

SAINTE-ROSE Christian — **Neurochirurgie Pédiatrique**
CHU de MARTINIQUE
Tel : 0696 73 27 27

André CABIE — **Maladies Infectieuses**
CHU de MARTINIQUE
Tel : 05 96 55 23 01

Philippe CABRE — **Neurologie**
CHU de MARTINIQUE
Tel : 05 96 55 22 61

Raymond CESAIRE — **Bactériologie-Virologie-Hygiène option virologie**
CHU de MARTINIQUE
Tel : 05 96 55 24 11

Sébastien BREUREC — **Bactériologie &Vénérologie Hygiène hospitalière**
CHU de POINTE- À -PITRE/ABYMES
Tel : 05 90 89 12 80

Maryvonne DUEYMES-BODENES — **Immunologie**
CH de CAYENNE
Tel : 05 96 55 24 24

Annie LANNUZEL — **Neurologie**
CHU de POINTE- À -PITRE/ABYMES
Tel : 05 90 89 14 13

Louis JEHEL	**Psychiatrie Adulte** CHU de MARTINIQUE Tel : 05 96 55 20 44
Mathieu NACHER	**Epidémiologie** CH de CAYENNE Tel : 05 94 93 50 24
Michel CARLES	**Anesthésie-Réanimation** CHU de POINTE-A-PITRE/BYMES Tel :05 90 89 17 74
Magalie DEMAR-PIERRE	**Parasitologie et Infectiologue** CH de CAYENNE Tel : 05 94 39 53 09
Vincent MOLINIE	**Anatomie Cytologie Pathologique** CHU de MARTINIQUE Tel : 05 96 55 20 85/55 23 50
Philippe KADHEL	**Gynécologie-Obstétrique** CHU de POINTE-A-PITRE/ABYMES Tel : 0690 39 56 28
Jeannie HELENE-PELAGE	**Médecine Générale** Cabinet libéral au Gosier Tel : 05 90 84 44 40 - Fax : 05 90 84 78 90
MEJDOUBI Mehdi	**Radiologie et Imagerie** CHU de MARTINIQUE Tel : 0696 38 05 20
VENISSAC Nicolas	**Chirurgie Thoracique Et cardiovasculaire** CHU de MARTINIQUE Tel : 0696 03 86 87
DJOSSOU Félix	**Maladies Infectieuses Et tropicales** CH de CAYENNE Tél : 0694 20 84 20
Christophe DELIGNY	**Gériatrie et biologie du vieillissement** CHU de MARTINIQUE Tel : 05 96 55 22 55
Narcisse ELENGA	**Pédiatrie** CH de CAYENNE Tel : 06 94 97 80 48

Karim FARID — **Médecine Nucléaire**
CHU de MARTINIQUE
Tel : 05 96 55 24 61

Moustapha DRAME — **Epidémiologie Economie de la Santé**
CHU de MARTINIQUE

Professeurs des Universités Associé

Franciane GANE-TROPLENT — **Médecine générale**
Cabinet libéral les Abymes
Tel : 05 90 20 39 37

Maître de Conférences des Universités - Praticiens Hospitaliers

Jocelyn INAMO — **Cardiologie**
CHU de MARTINIQUE
Tel : 05 96 55 23 72 - Fax : 05 96 75 84 38

Fritz-Line VELAYOUDOM épse CEPHISE — **Endocrinologie**
CHU de POINTE- À -PITRE/ABYMES
Tel : 05 90 89 13 03

Marie-Laure LALANNE-MISTRIH — **Nutrition**
CHU de POINTE- À -PITRE/ABYMES
Tel : 05 90 89 13 00

TABUE TEGUO Maturin — **Médecine interne : Gériatrie et biologie Du vieillissement**
CHU de POINTE- À -PITRE/ABYMES
Tel : 0690 30 85 04

GELU-SIMEON Moana — **Gastroentérologie**
CHU de POINTE-A-PITRE/ABYMES
Tel : 06 90 83 78 40 - Fax : 05 90 75 84 38

BACCINI Véronique — **Hématologie, Transfusion**
CHU de POINTE- À - PITRE/ABYMES
Tel : 05 90 89 12 77

MASSE Franck — **Médecine Générale**
Tél : 0596 56 13 23

CARRERE Philippe — **Médecine Générale**
Tél : 0690 99 99 11

Chefs de Clinique des Universités - Assistants des Hôpitaux

DARCHE Louis — **Chirurgie Générale et Viscérale**
CHU de MARTINIQUE
Tel : 05 96 55 21 01

LEFEVRE Benjamin — **Maladies Infectieuses**
CHU de POINTE-A-PITRE
Tel : 06 90 51 52 47

BUTORI Pauline — **ORL**
CHU de POINTE-A-PITRE
Tel : 0590 89 14 50

BONIFAY Timothée — **Médecin Générale**
CHU de Cayenne Croix rouge
Tel : 06 90 99 99 11

DURTETTE Charlotte — **Médecine Interne**
CHU de MARTINIQUE
Tel : 05 96 55 22 55

RENARD Guillaume — **Chirurgie Orthopédique**
CHU de MARTINIQUE
Tel : 06 96 26 27 33

GUERIN Meggie — **Parasitologie et Mycologie**
CH de CAYENNE
Tel : 06 70 86 88 91

SYLVESTRE Emmanuelle — **Maladies Infectieuses**
CHU de MARTINIQUE
Tel : 06 20 60 31 36

POUY Sébastien — **Cardiologie**
CHU de MARTINIQUE
Tel : 06 66 44 56 15

DEBBAGH Hassan — **Urologie**
CHU de MARTINIQUE
Tel : 0596 55 22 71

HENNO Florent — **Anesthésiologie/Réanimation**
CHU de POINTE-A-PITRE/ABYMES

Tel : 06 37 85 15 28

BANCEL Paul — **ORL**
CHU de POINTE- À -PITRE/ABYMES
Tel : 05 90 93 46 16

MONFORT Astrid — **Cardiologie**
CHU de MARTINIQUE
Tel : 05 96 55 23 72

PARIS Eric — **Réanimation**
CHU POINTE-A-PITRE/ABYMES
Tel : 05 94 39 53 39

JEREMIE Jean-Marc — **Psychiatrie**
CHU de MARTINIQUE
Tel : 05 96 55 20 44

TRAMIER Ambre — **Gynécologie Obstétrique**
CHU de POINTE- À –PITRE/ABYMES
Tel : 0590 89 19 89

PIERRE-JUSTIN Aurélie — **Neurologie**
CHU POINTE-A-PITRE/ABYMES
Tel : 05 90 89 13 40

MOUREAUX Clément — **Urologie**
CHU POINTE-A-PITRE/ABYMES
Tel : 05 90 89 13 95

CARPIN Jamila — **Médecine Générale**
Cabinet du Dr GANE-TROPLENT Franciane
Tel : 0690 72 12 04

PLACIDE Axiane — **Médecine Générale**
CHU de MARTINIQUE
Tel : 0690 30 75 19

NIEMETZKY Florence — **Médecine Générale**
CH de CAYENNE
Tel : 0694 16 15 31

BLAIZOT Romain — **Dermatologie**
CH de CAYENNE
Tel : 0694 08 74 46

Remerciements

A Monsieur le Professeur Felix Djossou,

Vous me faites l'honneur de présider le jury de ma thèse.
Je vous remercie pour vos idées pertinentes et votre disponibilité à mon égard.

A Monsieur le Docteur Hatem Kallel,

Je vous remercie de m'avoir proposé et diriger cette thèse, ce fut un enrichissement pour moi.
Je vous suis également reconnaissante pour vos sages conseils, votre bienveillance et vos encouragements soutenus.

A Monsieur le Professeur Michel Carles,

Je vous remercie de faire partie de mon jury, c'est un honneur.
Vous avez suivi et orienté mon parcours.
Travailler avec vous fut un réel plaisir.

A Monsieur le Docteur Didier Hommel,

Je vous remercie de faire parti de mon jury de thèse.
J'ai beaucoup appris de vos connaissances et vous remercie pour votre acceuil.

A Madame le Professeur Magali Demar,

Je vous remercie de faire partie de mon jury de thèse.
Je serai honorer de recevoir votre opinion sur ce sujet.

A Monsieur le Professeur Pierre Couppie,

Je vous remercie de faire parti de mon jury de thèse , et de l'intérêt que vous y portez.
J'en suis honorée.

A mes Parents,

Vous m'avez soutenu sans faille et encouragé tout au long de mes études, dans les bons comme les moments les plus difficiles,
Merci de m'avoir ouvert de multiples portes sur les différents aspects de la vie, matérielle et spirituelle.
Votre amour pour nous quatre est sans limite.

A mes frères et sœurs,

Mes compagnons de vie depuis toujours,
On a fait les quatre cents coups ensemble,
C'est grâce à votre soutien que j'ai pu affronter les épreuves,
Vous êtes ma source.

A ma tante Annie,

Tu es un modèle d'intelligence et de générosité,
Tu m'as soutenue et encouragée pour chaque étape difficile,
Je suis fière d'être ta nièce.

A ma grand-mère, Mina,

Tu as toujours été à mon écoute,
Tu m'as transmis ta joie de vivre et ta spontanéité.
Je ne t'oublie pas.

A Marjorie et Sébastien,

La vie peut prendre de nouveaux chemins, mais les bons souvenirs restent et l'affection que je vous porte ne s'effacera jamais.

A mes Amies et amis de Cannes et Nice,

J'ai partagé de merveilleux moments avec vous et ne vous oublie pas, Zezette, Abdi, Chachou, Annette, Pouline, Amby, Marichou, Florence, Julien, Poussin, Morvan et Charlouné…

A mes amies et amis des Antilles (et Paris!),

Cette période fut très riche en rencontres sincères et enrichissantes, vous êtes mon soleil des Caraibes.
à Emmachou, les deux Jules, Arthuro ,Arthur, Charles, Alexis et Victoire, Laura et Cindia (et Lollie) , Pascale et Jean luc, Ronnie, Diane et Caroline, Thierry et Vidian, Maria…

Merci à tous les co internes et les différents chefs qui m'ont enrichie de leur savoir et qui ont fait de mon internat une école de vie.

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 baumanii*

CRE= carbapenem-resistant Enterobacteriaceae

STM= *Stenotrophomonas maltophila*

MRSA= methicillin-résistant *Staphylococcus aureus*

ABRI= *Acinetobacter baumanii* 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 independants 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 facteur indépendants associés à la mortalité à J28étaient la catégorie non traumatique à l'admission et le choc septique le jour de l'ISR.

Table de matières

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 from1 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 sub-groups, 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 2353admissions 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).

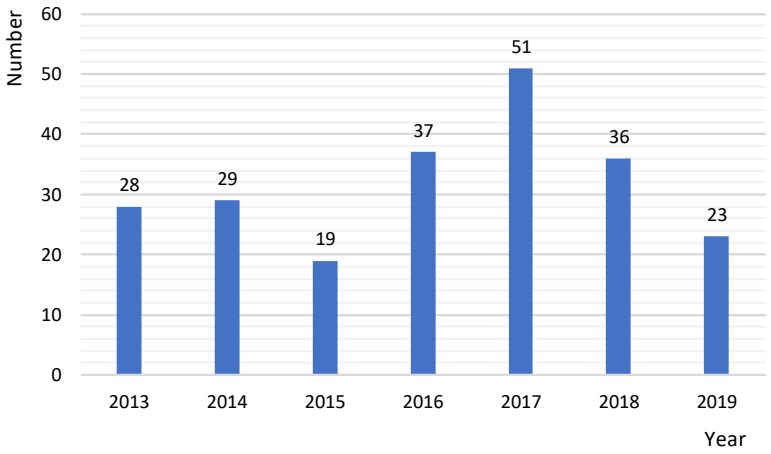

Figure 1: The incidence of ICU-BSI according to the year of the study.

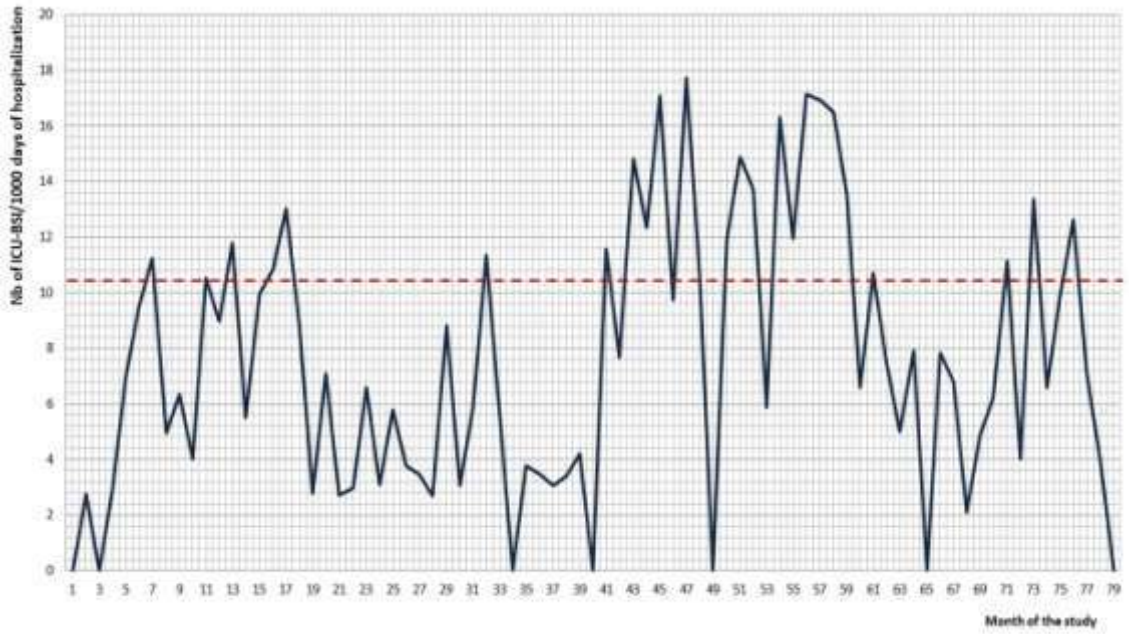

Figure 2: The monthly analysis of the number of ICU-BSI /1000 days of hospitalization.

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**
Escherichia coli	10 (52.6%)	9 (47.4%)	19 (100%)
Klebsiella pneumoniae	11 (16.2%)	57 (83.8%)	68 (100%)
Enterobacter cloacae	5 (18.5%)	22 (81.5%)	27 (100%)
Serratia marcescens	1 (16.7%)	5 (83.3%)	6 (100%)
Enterobacter aerogenes	0 (0%)	3 (100%)	3 (100%)
Enterobacter asburiae	1 (50%)	1 (50%)	2 (100%)
Citrobacter freundii	0 (0%)	1 (100%)	1 (100%)
Klebsiella oxytocae	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.*

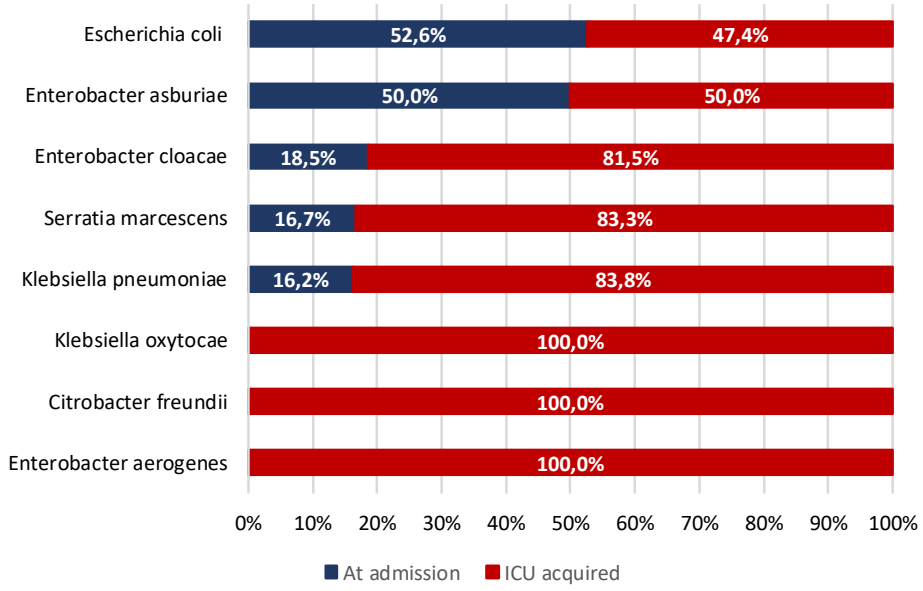

Figure 3: ESBL-PE carriage at admission and during ICU stay

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%)

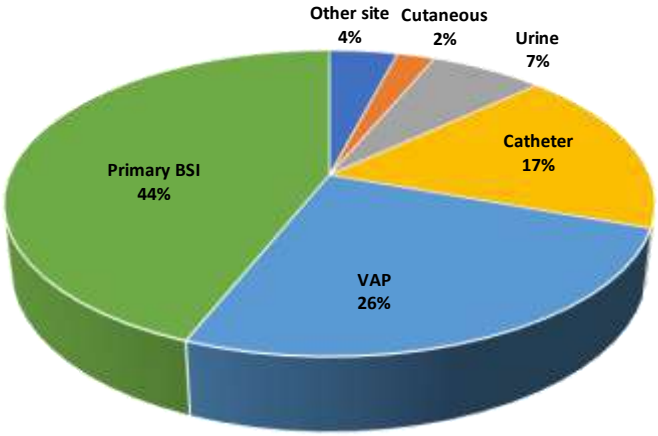

Figure 4 : The source of ICU-BSI

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**
Methicillin-Susceptible Staphylococcus aureus	21	8	9
Coagulase-negative staphylococci	16	6	7
Enterococcus faecalis	10	4	5
Methicillin-resistant Staphylococcus aureus	4	2	2
Streptococcus spp	5	2	2
Enterococcus faecium	1	0	0
Gram negative bacilli	**193**	**74**	**87**
Enterobacteracae	**151**	**58**	**68**
Klebsiella pneumoniae	65	25	29
Enterobacter cloacae	32	12	14
Escherichia coli	16	6	7
Enterobacter aerogenes	14	5	6
Serratia marcescens	9	3	4
Citrobacter koseri	6	2	3
Enterobacter asburiae	2	1	1
Klebsiella varicola	2	1	1
Proteus mirabilis	1	0	0
Pantoea dispersa	1	0	0
Morganella morganii	1	0	0
Citrobacter yougae	1	0	0
Citrobacter freundii	1	0	0
Non fermentative Gram negative bacilli	**42**	**16**	**19**
Pseudomonas aeruginosa	19	7	9
Acinetobacter baumannii	11	4	5
Acinetobacter nosocomialis	5	2	2
Aeromonas hydrophila	2	1	1
Stenotrophomonas maltophilia	2	1	1
Acinetobacter xylosoxidans	1	0	0
Burkholderia cepacia	2	1	1
Candida spp	**10**	**4**	**5**
Candida parapsilosis	5	2	2
Candida albicans	3	1	1
Candida tropicalis	1	0	0
Candida glabrata	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%)**
Staphylococcus aureus	3 (2.7%)	7 (10%)	12 (26.7%)	2 (10.5%)	1 (6.7%)	25 (9.5%)
Coagulase-negative staphylococci	12 (10.6%)	0 (0%)	2 (4.4%)	0 (0%)	2 (13.3%)	16 (6.1%)
Enterococcus faecalis	6 (5.3%)	0 (0%)	2 (4.4%)	1 (5.3%)	1 (6.7%)	10 (3.8%)
Streptococcus Spp	3 (2.7%)	0 (0%)	1 (2.2%)	1 (5.3%)	0 (0%)	5 (1.9%)
Enterococcus faecium	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%)**
Enterobacteriacae	**63 (55.8%)**	**48 (68.6%)**	**18 (40%)**	**13 (68.4%)**	**9 (60%)**	**151 (57.6%)**
Klebsiella pneumoniae	21 (18.6%)	24 (34.3%)	9 (20%)	8 (42.1%)	3 (20%)	65 (24.8%)
Enterobacter cloacae	14 (12.4%)	14 (20%)	2 (4.4%)	0 (0%)	2 (13.3%)	32 (12.2%)
Escherichia coli	8 (7.1%)	1 (1.4%)	0 (0%)	4 (21.1%)	3 (20%)	16 (6.1%)
Enterobacter aerogenes	8 (7.1%)	1 (1.4%)	4 (8.9%)	1 (5.3%)	0 (0%)	14 (5.3%)
Serratia marcescens	3 (2.7%)	5 (7.1%)	1 (2.2%)	0 (0%)	0 (0%)	9 (3.4%)
Citrobacter koseri	3 (2.7%)	2 (2.9%)	1 (2.2%)	0 (0%)	0 (0%)	6 (2.3%)
Enterobacter asburiae	1 (0.9%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)	2 (0.8%)
Klebsiella varicola	1 (0.9%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)
Citrobacter freundii	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Citrobacter yougae	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Morganella morganii	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (6.7%)	1 (0.4%)
Pantoea dispersa	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Proteus mirabilis	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%)**
Pseudomonas aeruginosa	5 (4.4%)	9 (12.9%)	4 (8.9%)	0 (0%)	1 (6.7%)	19 (7.3%)
Acinetobacter baumannii	6 (5.3%)	4 (5.7%)	1 (2.2%)	0 (0%)	0 (0%)	11 (4.2%)
Acinetobacter nosocomialis	4 (3.5%)	0 (0%)	1 (2.2%)	0 (0%)	0 (0%)	5 (1.9%)
Aeromonas hydrophila	0 (0%)	0 (0%)	1 (2.2%)	0 (0%)	1 (6.7%)	2 (0.8%)
Stenotrophomonas maltophilia	1 (0.9%)	1 (1.4%)	0 (0%)	0 (0%)	0 (0%)	2 (0.8%)
Acinetobacter xylosoxidans	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Burkholderia cepacia	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%)**
Candida spp	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%)**
Clostridium	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.4%)
Haemophilus Influenzae	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.

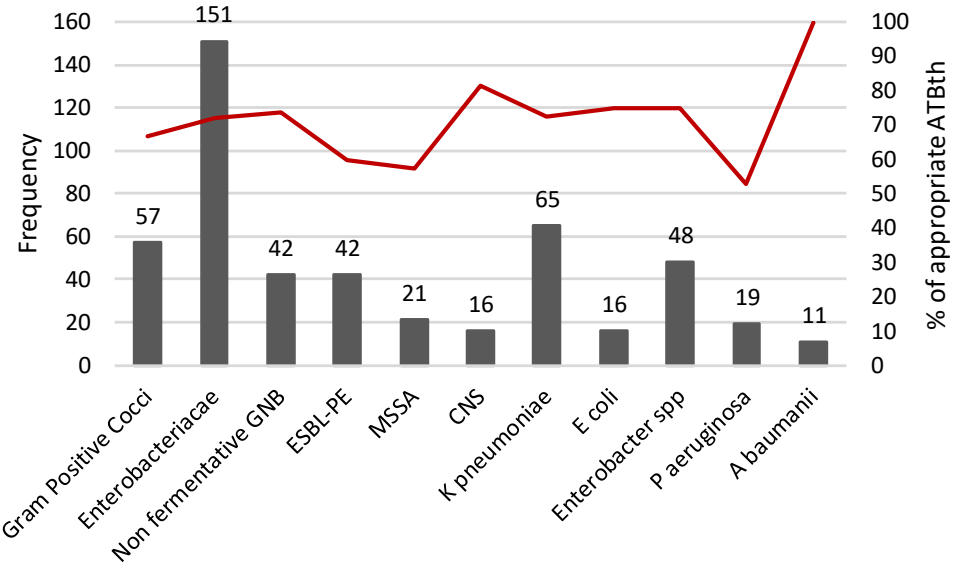

Figure 5: Appropriateness of initial antibiotherapy according to the responsible microorganism

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

	ICU-BSI caused by ESBL-PE		ICU-BSI caused by non ESBL-PE		p
Variable	**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
Enterobacteriacae	39	39 (100%)	184	86 (46.7%)	0.000
ESBL-PE	39	39 (100%)	184	0 (0%)	0.000
Methicillin sensitive *staphylococcus aureus*	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-*E coli* carriage	18	1	1	0.92	0.06	1	1	0.92
ESBL-P-*K pneumoniae* carriage	64	29	0.9	0.8	0.41	0.98	0.95	0.7
ESBL-P-*Enterobacter Spp* 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.

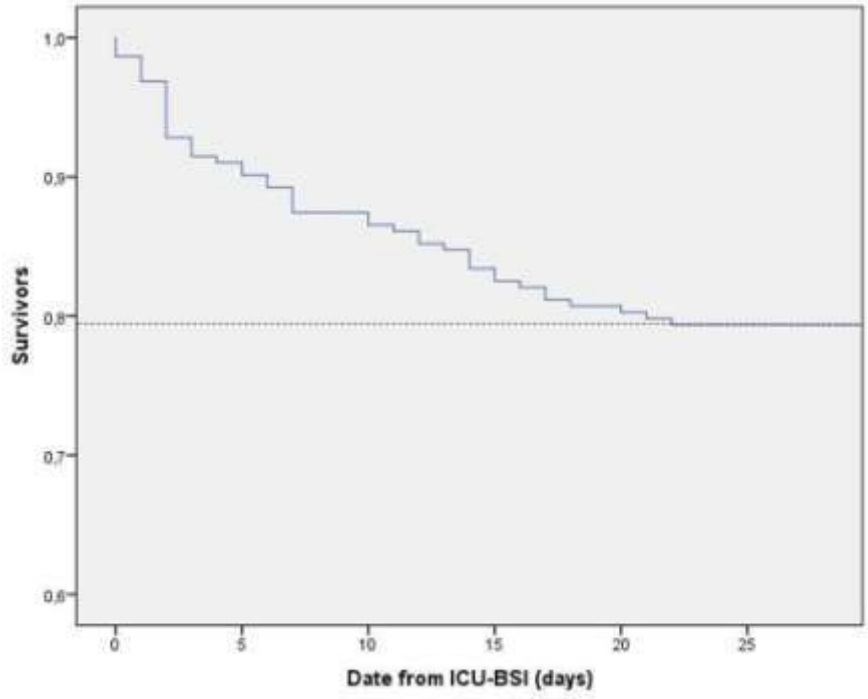

Figure 6: Mortality at day 28 in patients with ICU-BSI

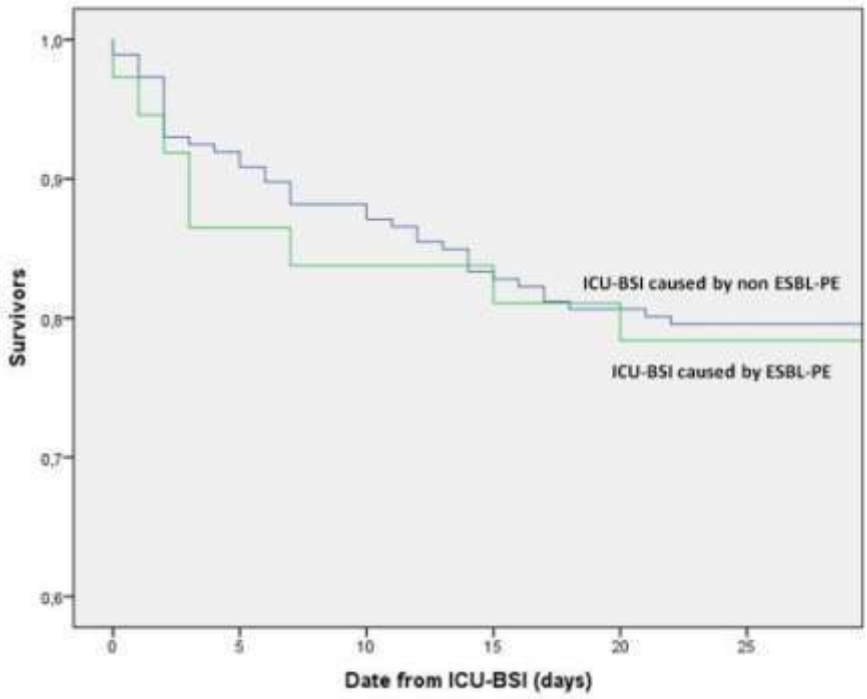

Figure 7: Mortality at day 28 in patients with ICU-BSI caused by ESBL-PE and non ESBL-PE (Log-Rank=ns)

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).

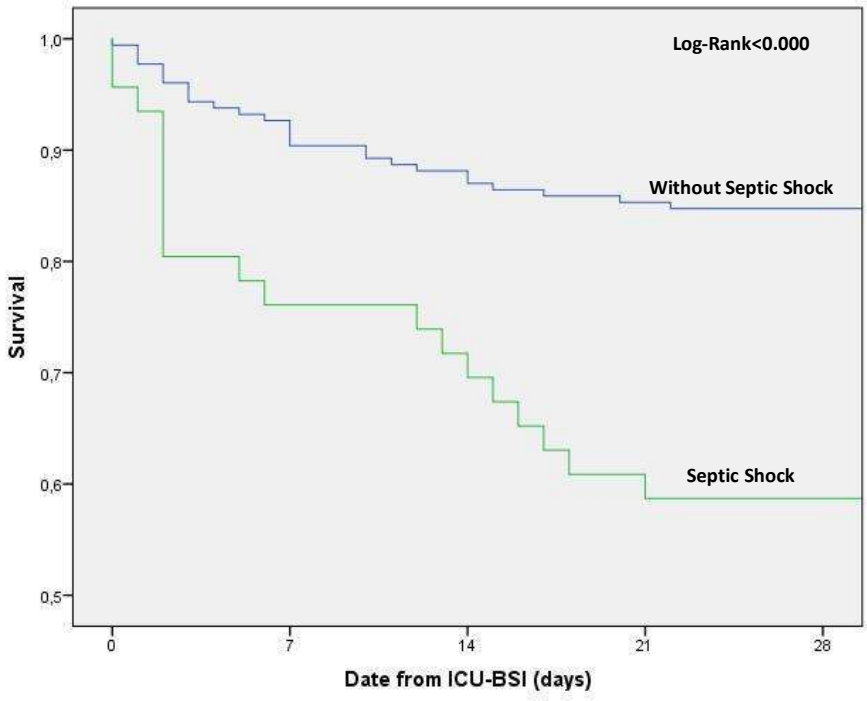

Figure 8: Mortality at day 28 in patients with ICU-BSI with and without associated septic shock (Log-Rank<0.0001)

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 *S aureus*	18.2	reference			
Enterobacteriacae	17.3	0.255	0.341	4.614	0.732
Klebsiella pneumoniae	9.2	0.245	0.114	1.772	0.245
Enterobacter spp	14.9	0.788	0.204	3.033	0.728
Escherichia coli	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
Pseudomonas aeruginosa	10.5	0.529	0.086	3.275	0.489
Acinetobacter baumannii	9.1	0.450	0.044	4.596	0.492
Candida spp	40.0	3.000	0.567	15.867	0.186
Coagulase-negative staphylococci	33.3	2.250	0.490	10.341	0.292

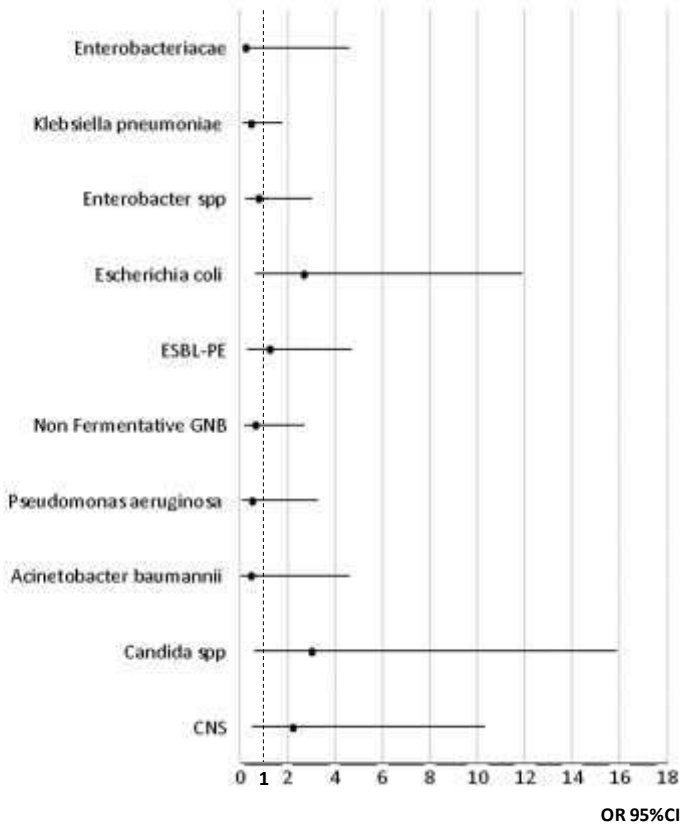

Figure 9: The mortality at day 28 according to the causative organism

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 micoorganisms were dominated by *Enterobacteriae* (68%) and an ESBL-PE was isolated in 24% of cases. Factors significantly associated toICU-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.

References

[1] Bassetti M, Righi E, Carnelutti A. Bloodstream infections in the Intensive Care Unit. Virulence 2016;7:267–79. https://doi.org/10.1080/21505594.2015.1134072.

[2] Adrie C, Garrouste-Orgeas M, Ibn Essaied W, Schwebel C, Darmon M, Mourvillier B, et al. Attributable mortality of ICU-acquired bloodstream infections: Impact of the source, causative micro-organism, resistance profile and antimicrobial therapy. Journal of Infection 2017;74:131–41. https://doi.org/10.1016/j.jinf.2016.11.001.

[3] Vincent J-L. International Study of the Prevalence and Outcomes of Infection in Intensive Care Units. JAMA 2009;302:2323. https://doi.org/10.1001/jama.2009.1754.

[4] Prowle JR, Echeverri JE, Ligabo EV, Sherry N, Taori GC, Crozier TM, et al. Acquired bloodstream infection in the intensive care unit: incidence and attributable mortality. Crit Care 2011;15:R100. https://doi.org/10.1186/cc10114.

[5] Garrouste-Orgeas M, Timsit JF, Tafflet M, Misset B, Zahar J-R, Soufir L, et al. Excess Risk of Death from Intensive Care Unit--Acquired Nosocomial Bloodstream Infections: A Reappraisal. Clinical Infectious Diseases 2006;42:1118–26. https://doi.org/10.1086/500318.

[6] Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients. Excess length of stay, extra costs, and attributable mortality. JAMA 1994;271:1598–601. https://doi.org/10.1001/jama.271.20.1598.

[7] Timsit J-F, Laupland KB. Update on bloodstream infections in ICUs: Current Opinion in Critical Care 2012;18:479–86. https://doi.org/10.1097/MCC.0b013e328356cefe.

[8] Russotto V, Cortegiani A, Graziano G, Saporito L, Raineri SM, Mammina C, et al. Bloodstream infections in intensive care unit patients: distribution and antibiotic resistance of bacteria. Infect Drug Resist 2015;8:287–96. https://doi.org/10.2147/IDR.S48810.

[9] Timsit J-F, Soubirou J-F, Voiriot G, Chemam S, Neuville M, Mourvillier B, et al. Treatment of bloodstream infections in ICUs. BMC Infect Dis 2014;14:489. https://doi.org/10.1186/1471-2334-14-489.

[10] Liu M, Li M, Wu L, Song Q, Zhao D, Chen Z, et al. Extended-spectrum β-lactamase-producing E. coli septicemia among rectal carriers in the ICU: Medicine 2018;97:e12445. https://doi.org/10.1097/MD.0000000000012445.

[11] Ammerlaan HSM, Harbarth S, Buiting AGM, Crook DW, Fitzpatrick F, Hanberger H, et al. Secular trends in nosocomial bloodstream infections: antibiotic-resistant bacteria

increase the total burden of infection. Clin Infect Dis 2013;56:798–805. https://doi.org/10.1093/cid/cis1006.

[12] Kim B-N, Woo J-H, Kim M-N, Ryu J, Kim YS. Clinical implications of extended-spectrum β-lactamase-producing Klebsiella pneumoniae bacteraemia. Journal of Hospital Infection 2002;52:99–106. https://doi.org/10.1053/jhin.2002.1288.

[13] Schwaber MJ, Navon-Venezia S, Kaye KS, Ben-Ami R, Schwartz D, Carmeli Y. Clinical and Economic Impact of Bacteremia with Extended- Spectrum- -Lactamase-Producing Enterobacteriaceae. Antimicrobial Agents and Chemotherapy 2006;50:1257–62. https://doi.org/10.1128/AAC.50.4.1257-1262.2006.

[14] Paterson DL, Ko W-C, Gottberg AV, Mohapatra S, Casellas JM, Goossens H, et al. Antibiotic Therapy for Klebsiella pneumoniae Bacteremia: Implications of Production of Extended-Spectrum b-Lactamases n.d.:7.

[15] Tabah A, Koulenti D, Laupland K, Misset B, Valles J, Bruzzi de Carvalho F, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med 2012;38:1930–45. https://doi.org/10.1007/s00134-012-2695-9.

[16] Vallés J, Calbo E, Anoro E, Fontanals D, Xercavins M, Espejo E, et al. Bloodstream infections in adults: importance of healthcare-associated infections. J Infect 2008;56:27–34. https://doi.org/10.1016/j.jinf.2007.10.001.

[17] Prowle JR, Echeverri JE, Ligabo EV, Sherry N, Taori GC, Crozier TM, et al. Acquired bloodstream infection in the intensive care unit: incidence and attributable mortality. Crit Care 2011;15:R100. https://doi.org/10.1186/cc10114.

[18] Timsit J-F, Soubirou J-F, Voiriot G, Chemam S, Neuville M, Mourvillier B, et al. Treatment of bloodstream infections in ICUs. BMC Infect Dis 2014;14:489. https://doi.org/10.1186/1471-2334-14-489.

[19] Barnett AG, Page K, Campbell M, Martin E, Rashleigh-Rolls R, Halton K, et al. The increased risks of death and extra lengths of hospital and ICU stay from hospital-acquired bloodstream infections: a case–control study. BMJ Open 2013;3:e003587. https://doi.org/10.1136/bmjopen-2013-003587.

[20] Schwaber MJ, Carmeli Y. Mortality and delay in effective therapy associated with extended-spectrum -lactamase production in Enterobacteriaceae bacteraemia: a systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy 2007;60:913–20. https://doi.org/10.1093/jac/dkm318.

[21] Tumbarello M, Sanguinetti M, Montuori E, Trecarichi EM, Posteraro B, Fiori B, et al. Predictors of Mortality in Patients with Bloodstream Infections Caused by Extended-Spectrum- -Lactamase-Producing Enterobacteriaceae: Importance of Inadequate Initial Antimicrobial Treatment. Antimicrobial Agents and Chemotherapy 2007;51:1987–94. https://doi.org/10.1128/AAC.01509-06.

[22] Nishie H. Guidelines for management of severe sepsis and septic shock. Okayama Igakkai Zasshi (Journal of Okayama Medical Association) 2013;125:153–7. https://doi.org/10.4044/joma.125.153.

[23] Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of Inappropriate Antimicrobial Therapy Results in a Fivefold Reduction of Survival in Human Septic Shock. Chest 2009;136:1237–48. https://doi.org/10.1378/chest.09-0087.

[24] Corona A, Bertolini G, Lipman J, Wilson AP, Singer M. Antibiotic use and impact on outcome from bacteraemic critical illness: the BActeraemia Study in Intensive Care (BASIC). Journal of Antimicrobial Chemotherapy 2010;65:1276–85. https://doi.org/10.1093/jac/dkq088.

[25] Actualisation des Précautions standard. SF2H n.d. https://sf2h.net/publications/actualisation-precautions-standard-2017.

[26] Munoz-Price LS, Poirel L, Bonomo RA, Schwaber MJ, Daikos GL, Cormican M, et al. Clinical epidemiology of the global expansion of Klebsiella pneumoniae carbapenemases. Lancet Infect Dis 2013;13:785–96. https://doi.org/10.1016/S1473-3099(13)70190-7.

[27] Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016;315:801–10. https://doi.org/10.1001/jama.2016.0287.

[28] Thouverez M, Talon D, Bertrand X. Control of Enterobacteriaceae producing extended-spectrum beta-lactamase in intensive care units: rectal screening may not be needed in non-epidemic situations. Infect Control Hosp Epidemiol 2004;25:838–41. https://doi.org/10.1086/502305.

[29] Calandra T, Cohen J, International Sepsis Forum Definition of Infection in the ICU Consensus Conference. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med 2005;33:1538–48. https://doi.org/10.1097/01.ccm.0000168253.91200.83.

[30] Martin MA, Pfaller MA, Wenzel RP. Coagulase-negative staphylococcal bacteremia. Mortality and hospital stay. Ann Intern Med 1989;110:9–16. https://doi.org/10.7326/0003-4819-110-1-9.

[31] Brun-Buisson C, Abrouk F, Legrand P, Huet Y, Larabi S, Rapin M. Diagnosis of central venous catheter-related sepsis. Critical level of quantitative tip cultures. Arch Intern Med 1987;147:873–7.

[32] Vallés J, Calbo E, Anoro E, Fontanals D, Xercavins M, Espejo E, et al. Bloodstream infections in adults: Importance of healthcare-associated infections. Journal of Infection 2008;56:27–34. https://doi.org/10.1016/j.jinf.2007.10.001.

[33] Cortegiani A, Russotto V, Graziano G, Saporito L, Raineri SM, Mammina C, et al. Bloodstream infections in intensive care unit patients: distribution and antibiotic resistance of bacteria. IDR 2015:287. https://doi.org/10.2147/IDR.S48810.

[34] De Rosa FG, Pagani N, Fossati L, Raviolo S, Cometto C, Cavallerio P, et al. The effect of inappropriate therapy on bacteremia by ESBL-producing bacteria. Infection 2011;39:555–61. https://doi.org/10.1007/s15010-011-0201-x.

[35] Lim SJ, Choi JY, Lee SJ, Cho YJ, Jeong YY, Kim HC, et al. Intensive care unit-acquired blood stream infections: a 5-year retrospective analysis of a single tertiary care hospital in Korea. Infection 2014;42:875–81. https://doi.org/10.1007/s15010-014-0651-z.

[36] Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370:1198–208. https://doi.org/10.1056/NEJMoa1306801.

[37] Vallés J, Alvarez-Lerma F, Palomar M, Blanco A, Escoresca A, Armestar F, et al. Health-care-associated bloodstream infections at admission to the ICU. Chest 2011;139:810–5. https://doi.org/10.1378/chest.10-1715.

[38] Laupland KB, Gregson DB, Zygun DA, Doig CJ, Mortis G, Church DL. Severe bloodstream infections: a population-based assessment. Crit Care Med 2004;32:992–7. https://doi.org/10.1097/01.ccm.0000119424.31648.1e.

[39] Laupland KB, Zygun DA, Davies HD, Church DL, Louie TJ, Doig CJ. Population-based assessment of intensive care unit-acquired bloodstream infections in adults: Incidence, risk factors, and associated mortality rate. Crit Care Med 2002;30:2462–7. https://doi.org/10.1097/00003246-200211000-00010.

[40] Soufir L, Timsit JF, Mahe C, Carlet J, Regnier B, Chevret S. Attributable morbidity and mortality of catheter-related septicemia in critically ill patients: a matched, risk-adjusted,

cohort study. Infect Control Hosp Epidemiol 1999;20:396–401. https://doi.org/10.1086/501639.

[41] Gahlot R, Nigam C, Kumar V, Yadav G, Anupurba S. Catheter-related bloodstream infections. Int J Crit Illn Inj Sci 2014;4:162–7. https://doi.org/10.4103/2229-5151.134184.

[42] Corona A, Bertolini G, Lipman J, Wilson AP, Singer M. Antibiotic use and impact on outcome from bacteraemic critical illness: the BActeraemia Study in Intensive Care (BASIC). J Antimicrob Chemother 2010;65:1276–85. https://doi.org/10.1093/jac/dkq088.

[43] Paiva J-A, Pereira JM, Tabah A, Mikstacki A, de Carvalho FB, Koulenti D, et al. Characteristics and risk factors for 28-day mortality of hospital acquired fungemias in ICUs: data from the EUROBACT study. Crit Care 2016;20:53. https://doi.org/10.1186/s13054-016-1229-1.

[44] Armand-Lefèvre L, Angebault C, Barbier F, Hamelet E, Defrance G, Ruppé E, et al. Emergence of imipenem-resistant gram-negative bacilli in intestinal flora of intensive care patients. Antimicrob Agents Chemother 2013;57:1488–95. https://doi.org/10.1128/AAC.01823-12.

[45] Lim CL, Spelman D. Mortality impact of empirical antimicrobial therapy in ESBL- and AmpC-producing Enterobacteriaceae bacteremia in an Australian tertiary hospital. Infection, Disease & Health 2019;24:124–33. https://doi.org/10.1016/j.idh.2019.02.001.

[46] Schwab F, Geffers C, Behnke M, Gastmeier P. ICU mortality following ICU-acquired primary bloodstream infections according to the type of pathogen: A prospective cohort study in 937 Germany ICUs (2006-2015). PLoS ONE 2018;13:e0194210. https://doi.org/10.1371/journal.pone.0194210.

[47] Kumar A, Ellis P, Arabi Y, Roberts D, Light B, Parrillo JE, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. Chest 2009;136:1237–48. https://doi.org/10.1378/chest.09-0087.

[48] Marra AR, Camargo LFA, Pignatari ACC, Sukiennik T, Behar PRP, Medeiros EAS, et al. Nosocomial bloodstream infections in Brazilian hospitals: analysis of 2,563 cases from a prospective nationwide surveillance study. J Clin Microbiol 2011;49:1866–71. https://doi.org/10.1128/JCM.00376-11.

[49] Tabah A, Koulenti D, Laupland K, Misset B, Valles J, Bruzzi de Carvalho F, et al. Characteristics and determinants of outcome of hospital-acquired bloodstream infections

in intensive care units: the EUROBACT International Cohort Study. Intensive Care Med 2012;38:1930–45. https://doi.org/10.1007/s00134-012-2695-9.

[50] Ziegler MJ, Pellegrini DC, Safdar N. Attributable mortality of central line associated bloodstream infection: systematic review and meta-analysis. Infection 2015;43:29–36. https://doi.org/10.1007/s15010-014-0689-y.

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)	ICU-BSI caused by BLSE-PE		ICU-BSI caused by non BLSE-PE		p
Parameter	**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	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
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	39	28 (71.8%)	184	89 (48.4%)	0.018
Bacteraemia at admission	28	7 (25%)	89	16 (18%)	0.950
Antibiotics at admission	39	35 (89.7%)	184	119 (64.7%)	0.004
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)	ICU-BSI caused by BLSE-PE		ICU-BSI caused by non BLSE-PE		p
Parameter	**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
Enterobacteriacae	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 S*taphylococcus aureus*	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)	Dead at 28 day		Alive at 28 day		p
Parameter	**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	46	32 (69.6%)	177	97 (54.8%)	0.183
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	46	3 (2 - 4)	177	2 (2 - 3)	0.087
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	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	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	46	24 (52.2%)	177	93 (52.5%)	0.964
BSI at admission	24	8 (33.3%)	93	15 (16.1%)	0.059
Antibiotics at admission	46	28 (60.9%)	177	126 (71.2%)	0.177
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)	Dead at 28 day		Alive at 28 day		p
Parameter	**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
Enterobacteriacae	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 S*taphylococcus aureus*	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.