Quantifying carriage of extended-spectrum beta-lactamase-producing enterobacteriaceae and subsequent ICU acquired infection in French Guiana

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THESE

Quantifying Carriage of Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae and subsequent ICU acquired infection in French Guiana

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5

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Table des matières

Liste des abréviations

ICU-AI	Intensive care unit acquired infection
SAPS II	Simplified Acute Physiology Score II
SOFA	Sequential Organ Failure Assessment
ICU	Intensive care unit
ESBL-E	Extended-spectrum β-lactamase-producing *Enterobacteriaceae*
ESBL-PE	ESBL-Producing *Enterobacteriaceae*
ESBL	Extended-Spectrum Beta-Lactamases
CI	Confidence Interval
FG	French Guiana
LOS	Length of stay
MDR-B	Multi-drug resistant bacteria
Pyo TIC-R	*Pseudomonas aeruginosa* resistant to Ticarcillin
ABB	*Acinetobacter baumanii*
CRE	Carbapenem-resistant *Enterobacteriaceae*
STM	*Stenotrophomonas maltophila*
MRSA	Methicillin Resistant *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
SPSS	Statistical Package for the Social Sciences
HIV	Human immunodeficiency virus
VAP	Ventilator associated pneumonia
ATB	Antibiotics
AMX-Clav	Amoxicillin-clavulanate
PIP-TAZ	Piperacillin Tazobactam,
3rd GC	Third Generation Cephalosporins
IMI	Imipenem
ICU LOS	ICU length of stay

Quantifying Carriage of Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae and subsequent ICU acquired infection in French Guiana

Introduction

Carriage of ESBL-Producing Enterobacteriaceae (ESBL-PE) carrying in ICU is responsible of increased mortality and morbidity. In this study, we were interested in quantifying ICU carriage and ICU-AI caused by ESBL-PE and whether carriage of ESBL-PE had an impact on ICU-AI.

Materials and methods

Our study is a prospective observational non-interventional work. It was conducted over 5 years period (Jan 2013–Dec 2017) in the medical-surgical intensive care unit of the Cayenne General Hospital.

Results

During the study period 1698 patients were admitted in our ICU. The median age of our patients was 44 years [28-60]. One or more comorbidity was recorded in 45.6% of patients. Immunodeficiency was recorded in 30.8% of patients.

One hundred fifty-nine patients (9.3%) were ESBL-PE carriers at admission to ICU and 208 patients acquired ESBL-PE carriage during ICU stay (13.5% of non ESBL carriers at admission). Among the 367 ESBL-PE carriers, 137 patients (37.3%) developed ICU-AI. By multivariable analysis, independent factors associated to the occurrence of ICU-AI were Trauma admission (p: 0.029; OR: 2.5 [1.1 -5.7]), Mechanical Ventilation > 48 hours (p:0.006; OR:17.5 [2.2 -136.7]), Tracheostomy (p: 0.006; OR: 4.6 [1.5 -13.9]), Renal Replacement Therapy (p: 0.030, OR: 2.5 [1.1 -5.9]), Arterial catheterization (p: 0.033, OR: 4.1 [1.1 -14.8]), Exposure to : AMX-Clav (p: 0.014; OR: 2.8 [1.2 -6.3]), to PIP-TAZ (p: 0.007; OR: 2.5 [1.3 -4.8]), to 3rd GC (p: 0.000; OR: 3.6 [1.8 -7.3]), and to Imipenem (p: 0.000; OR: 6.1 [2.8 -13.2]) during hospitalization. ICU-AI in ESBL-PE carriers was caused by an ESBL-PE in 39 cases (28.4%). Factors associated with ICU-AI caused by ESBL-PE in ESBL-PE carriers were trauma admission (p: 0.001; OR: 0.1 [0 -0.5]), Hemodynamic failure at admission (p: 0.005; OR: 4.2 [1.5 -11.4]), and Imipenem exposure prior to infection (p: 0.025; OR: 3.2 [1.2 -8.9]). The positive predictive value of ESBL-PE carriage to predict ESBL-PE as the causative germ of ICU-AI was 28.5%, and the negative predictive value was 84.3%.

Conclusion:

ESBL-PE carriage is frequently associated to ICU-AI, but, does not predict ESBL-PE as responsible germ of ICU-AI. Antibiotic exposure mainly to carbapenems is independent risk factor exposing to ICU-AI and to ICU-AI caused by ESBL-PE.

Résumé

Introduction
La colonisation à entérobactéries productrices de B-lactamase à Spectre Etendu (PE-BLSE) en réanimation est responsable d'une surmortalité et d'une surmorbidité. Le but de notre travail était de quantifier le portage de PE-BLSE en réanimation et à déterminer son impact sur les infections acquises en réanimation (IAR).

Matériels et méthodes
Notre étude est prospective observationnelle non interventionnelle. Il a été mené sur une période de 5 ans (janvier 2013 à décembre 2017) dans le service de réanimation polyvalente du Centre Hospitalier de Cayenne.

Résultats
Au cours de la période d'étude, 1698 patients ont été admis dans notre service. L'âge médian de nos patients était de 44 ans [28-60]. Une ou plusieurs comorbidités ont été enregistrées chez 45,6% des patients. Une immunodépression a été enregistrée chez 30,8% des patients.
Cinquante-neuf patients (9,3%) étaient porteurs de ES-BLSE à l'admission en réanimation et 208 patients ont acquis le portage pendant le séjour (13,5% des non-porteurs à l'admission). Parmi les 367 patients porteurs de ES-BLSE, 137 patients (37,3%) ont développé une IAR. Après analyse par régression logistique, les facteurs indépendants associés à la survenue d'une IAR étaient: patient traumatisé (p: 0,029; OR: 2,5 [1,1 - 5,7]), Ventilation Mécanique > 48 heures (p: 0,006; OR: 17,5 [2,2 à 136,7]), trachéotomie (p : 0,006; OR: 4,6 [1,5 -13,9]), épuration extra-rénale (p: 0,030, OR: 2,5 [1,1 - 5,9]), cathétérisme artériel (p: 0,033, OR: 4,1 [1,1 -14,8]), exposition à : AMX-Clav (p: 0,014; OR: 2,8 [1,2 -6,3]), à PIP-TAZ (p: 0,007; OR: 2,5 [1,3 -4,8]), aux C3G (p: 0,000; OR: 3,6 [1,8 à 7,3]) et à l'Imipenème (p: 0,000; OR: 6,1 [2,8 -13,2]) au cours de l'hospitalisation. L'IAR chez les patients porteurs d' ES-BLSE a été causée par une ES-BLSE dans 39 cas (28,4%). Les facteurs associés à l'IAR causée par une ES-BLSE chez les porteurs d' ES-BLSE étaient l'admission pour cause traumatique (p: 0,001; OR: 0,1 [0 -0,5]), défaillance hémodynamique à l'admission (p: 0,005; OR: 4,2 [1,5 -11,4]) et exposition à l'Imipenème avant l'infection (p: 0,025; OR: 3,2 [1,2 -8,9]). La valeur prédictive positive du portage d'ES-BLSE pour prédire qu'une IAR est causée par une ES-BLSE était de 28,5% et la valeur prédictive négative de 84,3%.

Conclusion :
Le portage d'ES-BLSE est souvent associé à la survenue d'IAR, mais ne prévoit pas que l'ES-BLSE en soient responsable. L'exposition aux antibiotiques notamment aux carbapenèmes est un facteur de risque indépendant de survenue d'IAR et de survenue d'IAR causée par une ES-BLSE.

Introduction

Extended-Spectrum Beta-Lactamases (ESBL) are enzymes that confer resistance to most beta-lactam antibiotics excluding carbapenems. They were reported since the early 80s in *Klebsiella pneumoniae* and *Escherichia coli*[1] and are now characterized asa serious threat problem in hospitalized patients and in the community [2]. Indeed, since they hydrolyse penicillins, cephalosporins, and aztreonam, antibiotic options in the treatment of ESBL-producing organisms are extremely limited.

Carriage of ESBL-Producing Enterobacteriaceae (ESBL-PE) in Intensive care unit (ICU) is increasing worldwide. It varies greatly from 2 to 49% [3–5]. At admission to ICU, at risk patients are those recently hospitalized especially in ICU or recently exposed to antibiotics mainly third generation cephalosporins or blactam/inhibitor combinations[5]. During hospitalization in ICU, patients can acquire ESBL-PE because of cross transmission from colonized to non-colonized patientsor in relation with antibiotic pressure. The significance of ICU-acquired ESBL-PE for patient outcome is controversial. Some studies have shown ICU-acquired ESBL-PE to be associated with high mortality, excessive length of ICU and hospital stay, and high hospital costs[6–8] .

When patient is carrying ESBL-PE, he can spread the bacteria to other patients (cross transmission) and he can develop infection caused by the same bacteria which will be difficult to treat. Indeed, in 17.6% of cases, intensive care unit acquired infection (ICU-AI) is caused by an ESBL-PE [9]. Risk factors to acquire infection caused by ESBL-PE during ICU stay are ESBL-PE carriage, chronic indwelling vascular hardware, age superior of 43 years, recent hospitalization and antibiotic exposure in the previous months [9, 10].

Despite the abundant literature in this field, there is no data regarding ESBL-PE carriage and ICU-AIin French Guiana (FG) or in the Guiana shield. FG is a French territory located in South-America where hospitals are managed according to European standards.

In this study, we were interested in quantifying ICU carriage and ICU-AI caused by ESBL-PE and whether carriage of ESBL-PE had an impact on ICU-AI.

Materials and methods

1-Setting and patients

Our study is a prospective observational non-interventional work. It was conducted over 5 years period (Jan 2013–Dec 2017) 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 roomswith a 1: 2.5 nurse-to-patient ratio. All patients havededicated 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.

All patients hospitalized in our ICU during the study period were included in this survey. For ICU-AI analysis, we included all patients with a first ICU admission (during the same hospital stay) of more than two calendar days. Patients hospitalized in 2012 and present in the unit in the 1/1/2013, were considered as admitted the 1/1/2013.

Screening for multi-drug resistant bacteria (MDR-B) carriage including Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* (ESBL-PE), Carbapenem-resistant *Enterobacteriaceae* (CRE), Methicillin Resistant Staphylococcus aureus (MRSA), *Pseudomonas aeruginosa* resistant to Ceftazidim (PYO CAZ-R), *Acinetobacter baumanii* resistant to imipenem (ABRI), and *Stenotrophomonas maltophila* (STM) is routinely performed 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 [11]. Contact precautions are used for patients with MDR bacteria recovered from screening cultures according to the "SFHH"[12].

2-Data collection

Data on all patients with or without ESBL-PE carriage were prospectively collected and, a detailed clinical profile of each patient was established.

The following data were collected: demographic characteristics, which included sex, age, type of admission, simplified acute physiology score (SAPS II) [6], organ dysfunction based on SOFA score at admission [13], can be identified as an acute change in total SOFA score ≥ 2 points[13], 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

Colonization was defined as the isolation of ESBL-PE from a surveillance culture or non-sterile clinical sample. Patients with ESBL-PE isolated within 48 hours of ICU admission were considered to be colonized upon admission. ESBL-PE isolated 48 hours after admission in patients with previous negative specimens were considered as ICU-acquired[3].

Daily colonization index was defined as the ratio of patients colonized with ESBL-PE to the total number of patients. Colonization pressure was determined as the sum of the daily proportion of patients in the unit colonized with ESBL-PE from ICU admission until ESBL-PE acquisition or until discharge in non ESBL-PE carriers [14].

4-Statistical analysis

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

The prevalence of ICU-acquired ESBL-PE carriage was estimated by subtracting theprevalence of ESBL-PE carriage at ICU admission from the prevalence of ESBL-PE carriage during hospitalization.

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 identify patients' characteristics associated with ICU-AI or ICU-AI caused by ESBL-PE in ESBL-PE carriers, 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.

Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic value of colonization index in predicting ESBL-PE acquisition during ICU stay. The area under the curve was estimated by the method of Hanley andMcNeill [15]. We calculatedthe sensibility, specificity, positive and negative predictive values, Youden test and the Qcoefficient of Yule to assess the diagnosis value of ESBL-PE carriage in predicting ESBL-PE related infection.

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 1698 patients were admitted in our ICU, and then, were included in our study. Seventeen patients of them were readmitted resulting in 1715 admissions. The mean number of admissions varies from 316 to 380 admissions per year and the occupancy rate per month was 84±14% (53-116). It was over 80% in 36 months (60% of the study period).

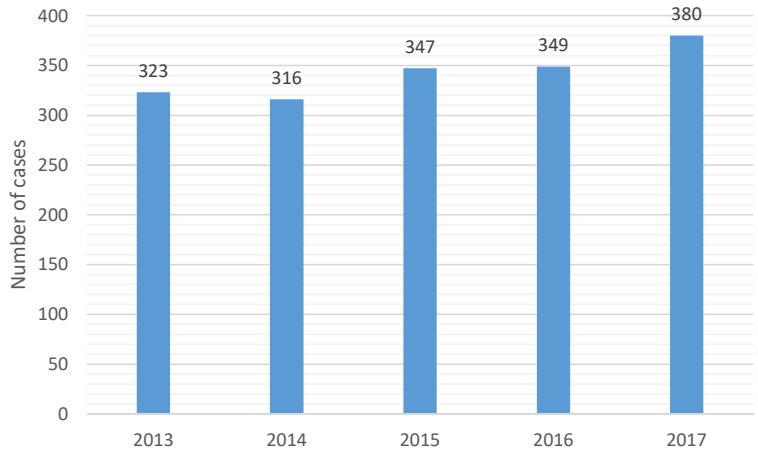

Figure 1: Distribution of our patients according to the year of hospitalization

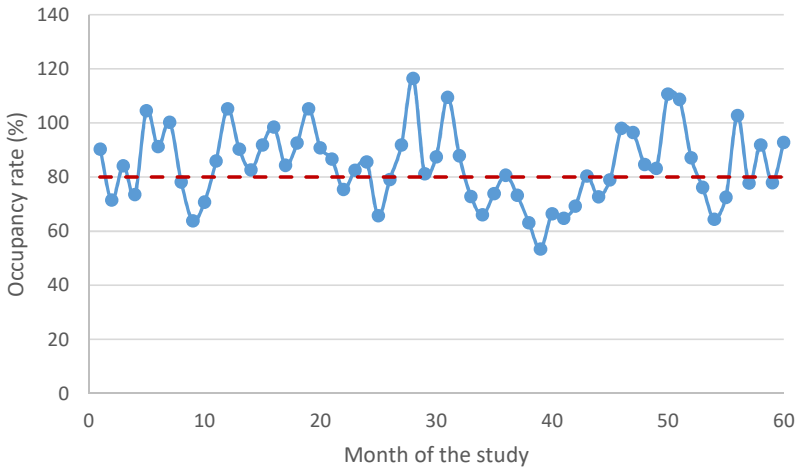

Figure 2: The occupancy rate of our unit during the 60 months of the study period.

The cumulative length of stay in ICU was 21145 days. The median length of stay (LOS) in ICU was 5 [3-12] (extremes 1 and 454 days), and it was more than two calendar days in 1349 patients (79.4%).

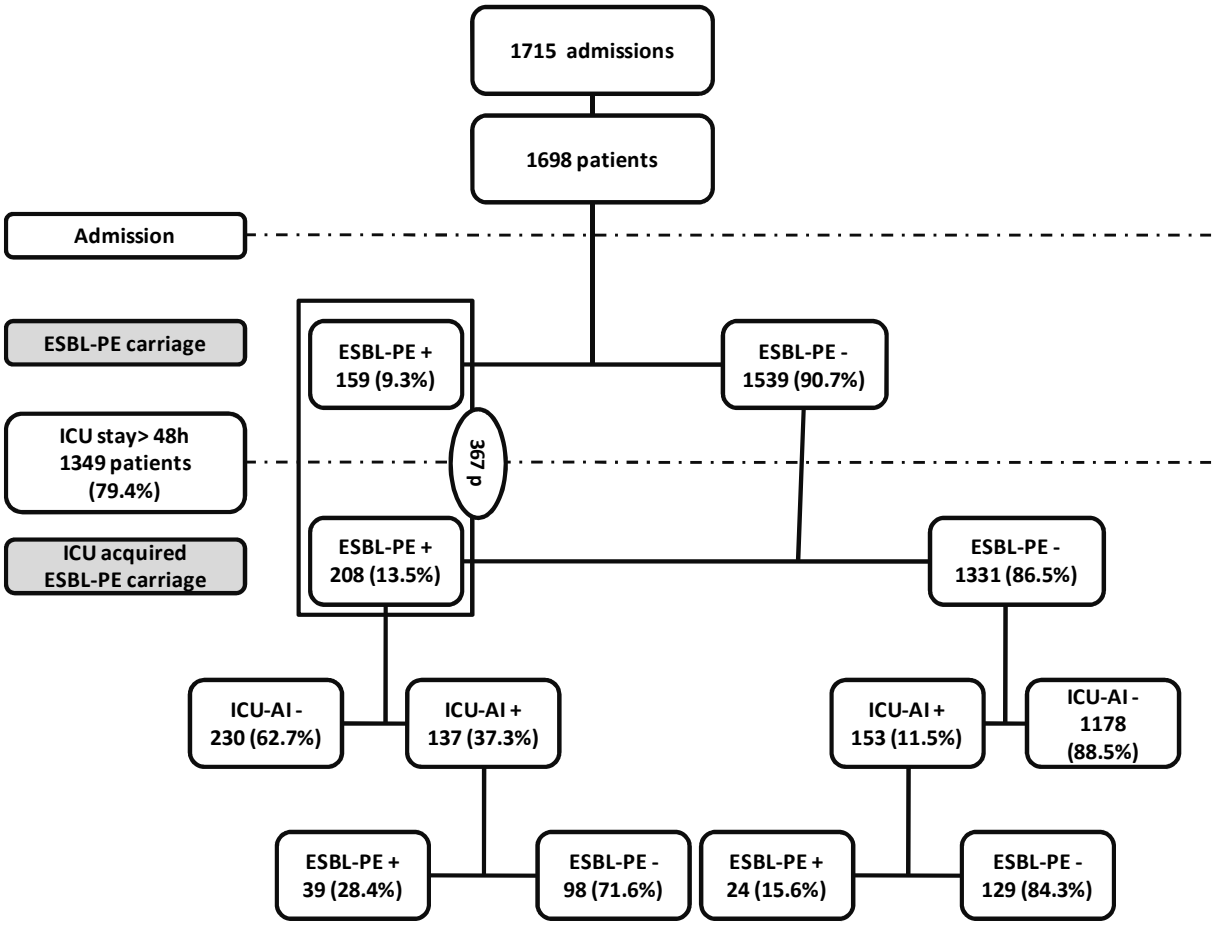

Figure 3: The Flow-Chart of our study

1-The study population

The median age of our patients was 44 years [28-60] and 60.7% of them were men. One or more comorbidity was recorded in 45.6% of patients. Immunodeficiency was recorded in 30.8% of patients and HIV infection was the mainly immunodeficiency origin. Epidemiological and clinical characteristics of all patients at admission to ICU are reported in Table I.

Table I: Epidemiologic and clinical parameters of the study population

Variable	Nb	Result
Age (years)	1698	44 [28-60]
Male gender	1698	1031 (60.7%)
BMI	1247	24.3 [21.37-28.17]
SAPS II	1698	42 [25-60]
Comorbidities	1698	775 (45.6%)
Arterial hypertension	1698	498 (29.3%)
Diabetes mellitus	1698	250 (14.7%)
Cancer	1698	117 (6.9%)
Immunodeficiency	1698	523 (30.8%)
Chronic renal failure	1698	89 (5.2%)
Chronic respiratory failure	1698	14 (0.8%)
Sickle cell disease	1698	44 (2.6%)
Type of admission	1698	
Medical	1698	1130 (66.5%)
Elective surgery	1698	82 (4.8%)
Emergent surgery	1698	486 (28.6%)
Traumatic	1698	378 (22.3%)
ATB during previous year	1698	201 (11.8%)
In the last 3 months	1698	104 (6.1%)
In the last 3 to 6 months	1698	60 (3.5%)
In the last 6 to 12 months	1698	37 (2.2%)
Hospitalization during previous year	1698	367 (21.6%)
In the last 3 months	1698	191 (11.2%)
In the last 3 to 6 months	1698	58 (3.4%)
In the last 6 to 12 months	1698	118 (6.9%)
Direct admission from emergency department	1698	1297 (76.4%)
Organ failure at admission	1698	
Hemodynamic	1698	703 (41.4%)
Respiratory	1698	900 (53.0%)
Neurologic	1698	804 (47.3%)
Kidney	1698	466 (27.4%)
Liver	1698	249 (14.7%)
Hematologic	1698	346 (20.4%)
Active infection at admission	1698	747 (44%)
Bacteraemia at admission	747	110 (14.8%)
Antibiotics at admission	1698	1037 (61.1%)
Amoxicillin clavulanate	1698	379 (22.3%)
Aminoglycosides	1698	386 (22.7%)
Piperacillin-Tazobactam	1698	281 (16.5%)
3rd generation cephalosporins	1698	270 (15.9%)
Imipenem	1698	61 (3.6%)
Fluoroquinolones	1698	110 (6.5%)
Metronidazole	1698	36 (2.1%)

2-Active infection at admission

Active infection at admission was recorded in 747 patients (44%) and bacteraemia was recorded in 110 of them (14.8). Antibiotics were prescribed in 61.1% of patients at admission to ICU. The sites of active infection diagnosed at admission to ICU are reported in Table IV.

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

Site of infection	Associated bacteraemia		Total
	No	Yes	
Pulmonary	375 (93.1%)	28 (6.9%)	403 (100%)
Intra-abdominal	86 (86%)	14 (14%)	100 (100%)
Cellulitis	48 (85.7%)	8 (14.3%)	56 (100%)
Neuromeningeal	37 (90.2%)	4 (9.8%)	41 (100%)
Urinary	33 (82.5%)	7 (17.5%)	40 (100%)
Dengue fever	12 (100%)	0 (0%)	12 (100%)
Non-defined	12 (100%)	0 (0%)	12 (100%)
Malaria	7 (100%)	0 (0%)	7 (100%)
Catheter related infection	6 (54.5%)	5 (45.5%)	11 (100%)
Leptospirosis	5 (100%)	0 (0%)	5 (100%)
Endometritis, Salpingitis	4 (80%)	1 (20%)	5 (100%)
Osteoarthritis	3 (100%)	0 (0%)	3 (100%)
Endocarditis	2 (50%)	2 (50%)	4 (100%)
Surgical site infection	2 (100%)	0 (0%)	2 (100%)
Ear, nose or throat infection	2 (66.7%)	1 (33.3%)	3 (100%)
Bacteraemia	0 (0%)	45 (100%)	45 (100%)

3-Therapeutic management in ICU

During ICU stay, 63.9% of patients received invasive mechanical ventilation, 9.5% received renal replacement therapy (RRT), 64.1% had central venous catheterization, and 59.1% had arterial catheterization. antibiotic exposure during ICU stay was recorded in 62.5% of patients. Therapeutic procedures and antibiotics exposure during hospitalization are reported in Table V.

Table V: Therapeutic management and antibiotics exposure during hospitalization.

Variable	Nb	Result
Mechanical ventilation	1698	1085 (63.9%)
Time from admission to MV	1085	0 [0-0]
MV more than 48 hours	1085	706 (65.1%)
Overall duration of MV (days)	1085	11681
Duration of MV without VAP (days)	1085	8881
Tracheostomy	55	55 (100%)
Renal replacement therapy	1698	162 (9.5%)
Time from admission to RRT (days)	162	0 [0-1]
Central venous catheterization	1698	1089 (64.1%)
Overall duration of CVC (days)	1089	14269
Duration of CVC without infection (days)	1089	13545
Arterial catheterization	1698	1004 (59.1%)
Overall duration of AC (days)	1004	8808
Duration of AC without infection (days)	1004	8710
ATB exposure during hospitalization	1698	1061 (62.5%)
Amoxicillin clavulanate	1698	384 (22.6%)
Aminoglycosides	1698	539 (31.7%)
Piperacillin-Tazobactam	1698	388 (22.9%)
3rd generation cephalosporins	1698	374 (22%)
Imipenem	1698	150 (8.8%)
Fluoroquinolones	1698	154 (9.1%)
Metronidazole	1698	51 (3%)

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

4-ESBL-PE carriage at admission and during ICU stay

One hundred fifty-nine patients (9.3%) were ESBL-PE carriers at admission to ICU. The main ESBL-PE isolated at admission were *E coli* (in 70 patients, 49.3% of isolated ESBL-PE, and 4.1% of all patients) and *K pneumoniae* (in 60 patients, 37.5% of isolated ESBL-PE, and 3.5% of all patients %). Isolated ESBL-PE at admission and during ICU stay are reported in Table VI.

Table VI: Data related to ESBL-PE carriage

Variable	Nb	Result
ESBL-PE carriage	1698	367 (21.6%)
ESBL-PE carriage at admission	1698	159 (9.3%)
ESBL-PE carriage acquired in ICU	1539	208 (13.5%)
Time from admission to ESBL-PE carriage*	208	11 [6-17]
Colonisation pressure	1698	135 [61-281]

** in patients with ICU acquired ESBL-PE carriage*

The diagnostic value of colonization index to predict ICU ESBL-PE carriage in non-carriers at admission is shown in Figure 4.

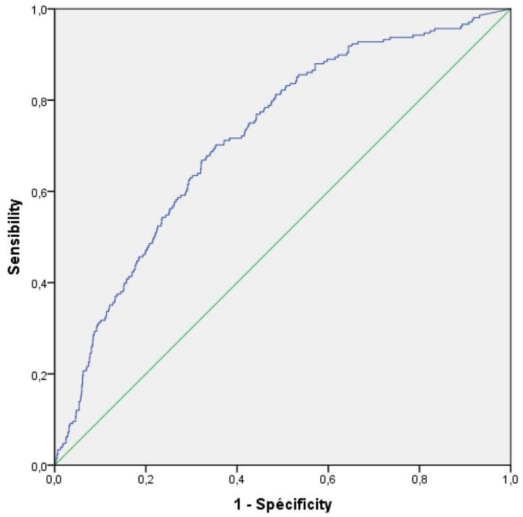

Figure4: ROC curve showing the diagnostic value of colonization pressure to predict ICU ESBL-PE carriage (AUC:0.72, p<0.001)

Two hundred and eight patients acquired ESBL-PE carriage during ICU stay (12.2% of all patients and 13.5% of non ESBL carriers at admission). The main ESBL-PE isolated on rectal swab samples during ICU stay were *K pneumoniae* (in 102 patients, 49.3% of isolated ESBL-PE, and 6.6% of non ESBL carriers at admission) and *E cloacae* (in 52 patients, 24.9% of isolated ESBL-PE, and 3.4% of non ESBL carriers at admission).

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

	At admission	ICU acquired	Total
Escherichia coli	71 (44.4%)	33 (15.8%)	103 (27.9%)
Klebsiella pneumoniae	60 (37.5%)	103 (49.3%)	162 (43.9%)
Enterobacter cloacae	24 (15%)	52 (24.9%)	76 (20.6%)
Serratia marcescens	1 (0.6%)	12 (5.7%)	13 (3.5%)
Enterobacter aerogenes	1 (0.6%)	3 (1.4%)	4 (1.1%)
Enterobacter asburiae	2 (1.3%)	3 (1.4%)	5 (1.4%)
Citrobacter freundii	0 (0%)	1 (0.5%)	1 (0.3%)
Citrobacter koseri	1 (0.6%)	1 (0.5%)	2 (0.6%)
Klebsiella oxytocae	0 (0%)	1 (0.5%)	1 (0.3%)
Total	160 (100%)	209 (100%)	369 (100%)

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

The median time to acquire ESBL-PE carriage in ICU was 4 days [0-12].

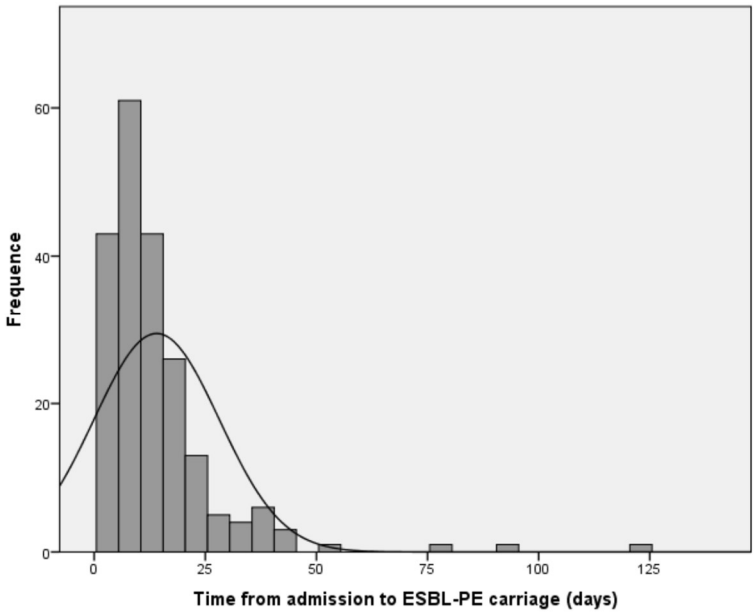

Figure 5: The mean time to acquire ESBL-PE carriage in our patients

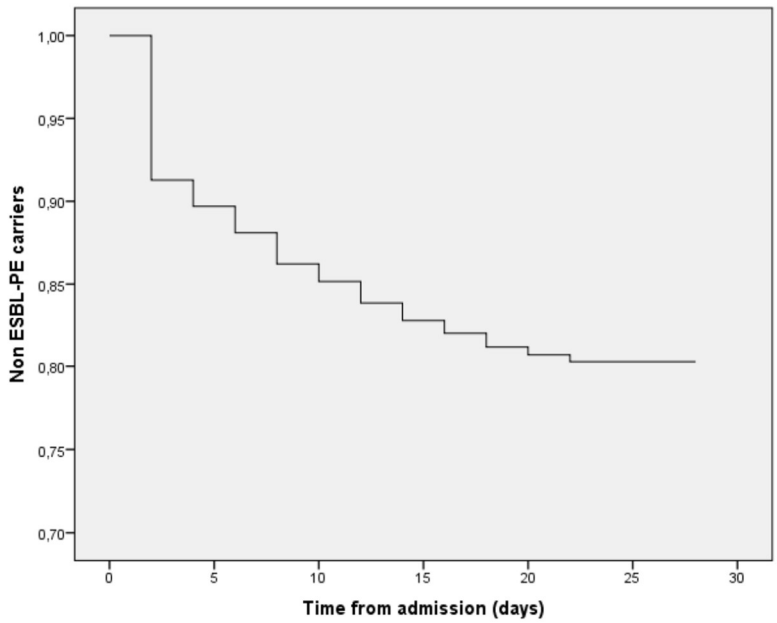

Figure 6: ESBL-PE carriage during the first 28 days of hospitalization.

The monthly colonization index was 35.9±11% in the average (ext. 13.9 - 66.1).

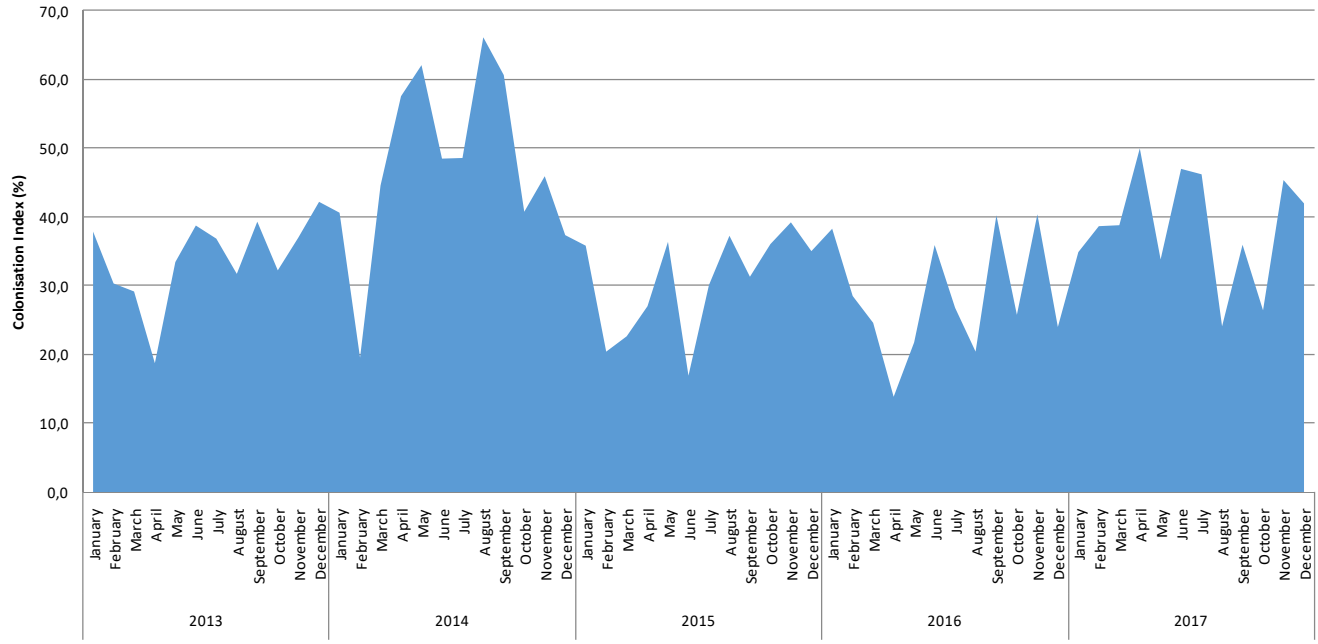

Figure 7: The monthly colonization index during the study period

5-Intensive Care Unit Acquired Infection

One or more episodes of ICU-AI is diagnosed in 290 patients (17.1%). It was caused by ESBL-PE in 63 patients (21.7%).

Table V: ICU-AI recorded in our patients and prior exposure to antibiotics

Variable	Nb	Result
ICU-AI	1698	290 (17.1%)
Ventilator associated pneumonia	125	125 (100%)
Density-incidence of VAP (/1000 days MV)	1085	14.1
Bacteraemia	182	182 (100%)
CVC related infection	1089	84 (7.7%)
Density-incidence of CVC-RI (/1000 days CVC)	1089	6.2
AC related infection	1004	34 (3.4%)
Density-incidence of AC-RI (/1000 days AC)	1004	3.9
Time from admission to ICU-AI	290	7 [4-12]
ICU-AI Caused by ESBL-PE	290	63 (21.7%)
Time from admission to ESBL-PE ICU-AI	63	11 [7-19]

CVC-RI: Central venous catheter related infection, AC-RI: Arterial catheter related infection

Antibiotic exposure prior to ICU-AI was observed in 214 patients (73.8% of patients with ICU-AI). The main recorded antibiotics were Amoxicillin clavulanate, aminoglycosides and Piperacillin-Tazobactam (Table VIII).

Table VIII: Antibiotics exposure prior to ICU-AI

Variable	Nb	Result
ATB exposure prior to ICU-AI	290	214 (73.8%)
Amoxicillin clavulanate	290	102 (35.2%)
Aminoglycosides	290	92 (31.7%)
Piperacillin-Tazobactam	290	60 (20.7%)
3rd generation cephalosporins	290	55 (19%)
Imipenem	290	32 (11%)
Fluoroquinolones	290	14 (4.8%)
Metronidazole	290	3 (1%)

6 -ICU acquired infection in ESBL-PE carriers

Among the 367 ESBL-PE carriers, 137 patients (37.3%) developed at least one episode of ICU-AI. Epidemiological and clinical data of patients with and without ICU-AI in ESBL-PE

carriers are reported in Appendix A. Thirty-nine patients (28.5%) developed one or more ICU-AI caused by ESBL-PE. The causative germ of the first episode of ICU-AI was ESBL-PE in 19% of cases. The table IX reports the frequency of ESBL-PE among the causative organisms of ICU-AI according to the episode of ICU-AI.

Table IX: Proportion of ICU-AI caused by ESBL-PE in ESBL-PE carriers'patients

Episode	Nb	% ESBL-PE
1	137	26 (19.0%)
2	66	11 (16.7%)
3	27	5 (18.5%)
4	13	3 (23.1%)
5	4	2 (50%)

** 8 patients developed 2 episodes of ICU-AI caused by ESBL-PE each*

Independent factors associated to the occurrence of ICU-AI in ESBL-PE carriers in multivariable analysis are listed in Table X.

Table X: Factors associated with ICU-AI in ESBL-PE carriers: multiple logistic regression model

Variable	P value	OR [95% CI]
Trauma admission	0.029	2.5 [1.1 -5.7]
MV > 48 hours	0.006	17.5 [2.2 -136.7]
Tracheostomy	0.006	4.6 [1.5 -13.9]
Renal Replacement Therapy	0.030	2.5 [1.1 -5.9]
Arterial catheterization	0.033	4.1 [1.1 -14.8]
Exposure to AMX-Clav during hospitalization	0.014	2.8 [1.2 -6.3]
Exposure to PIP-TAZ during hospitalization	0.007	2.5 [1.3 -4.8]
Exposure to 3rd GC during hospitalization	0.000	3.6 [1.8 -7.3]
Exposure to IMI during hospitalization	0.000	6.1 [2.8 -13.2]

MV: Mechanical Ventilation, AMX-Clav: Amoxicillin-clavulanate, PIP-TAZ: Piperacillin Tazobactam, 3rd GC: Third Generation Cephalosporins, IMI: Imipenem

Overall, 367 patients were ESBL-PE carriers. Among them 137 patients (37.3%) developed ICU-AI. It was caused by an ESBL-PE in 39 cases (28.4%). Epidemiological and clinical data

of patients with ICU-AI in ESBL-PE carriers according to the responsible germ resistance are reported in Appendix B. Independent factors associated to the occurrence of ICU-AI caused by ESBL-PE in ESBL-PE carriers in multivariable analysis are listed in Table XI

Table XI: Factors associated with ICU-AI caused by ESBL-PE in ESBL-PE carriers: multiple logistic regression model

Variable	P value	OR [95% CI]
Trauma admission	0.001	0.1 [0 -0.5]
Hemodynamic failure at admission	0.005	4.2 [1.5 -11.4]
IMI exposure prior to infection	0.025	3.2 [1.2 -8.9]

IMI: Imipenem

6 - Value of ESBL-PE carriage to predict ICU-AI caused by ESBL-PE

In non ESBL-PE carriers (1331 patients), 153 patients (11.5%) developed ICU-AI (11.5%). It was caused by an ESBL-PE in 24 patients (15.6%). The sensibility of ESBL-PE carriage to predict ESBL-PE as the causative germ of ICU-AI was 61.9%, specificity was 56.8%, Positive Predictive Value was 28.5%, Negative Predictive Value was 84.3%, Q coefficient of Yule was 0.36 (moderate range), and Youden index was 0.18.

7-Outcome

Mortality rate was 24.8% in the general population. It was 23.4% in ESBL-PE carriers with ICU-AI vs 23.5% in those without ICU-AI (p=ns). It was 28.2% in ESBL-PE carriers with ICU-AI caused by ESBL-PE vs 21.4% in ESBL-PE carriers with ICU-AI caused by non ESBL-PE (p=ns).

ICU length of stay was 50 days in ESBL-PE carriers with ICU-AI vs 9 days in those without ICU-AI (p<0.001). It was 37 days in ESBL-PE carriers with ICU-AI caused by ESBL-PE vs 32 days in ESBL-PE carriers with ICU-AI caused by non ESBL-PE (p=ns).

The outcome of our patients is reported in Table XII.

Table XII : Mortality and LOS in ICU

Variable	Nb	Result
ICU stay > 48 hours	1698	1349 (79.4%)
ICU LOS (days)	1698	5 [3-12]
Death	1698	421 (24.8%)
Death in the first 24 hours	421	71 (16.9%)

LOS: length of stay

Discussion

Our study gives information about colonization and infection to ESBL-PE in the context of south America and Amazonian region. The main findings of our study are that ESBL-PE carriage in our ICU is similar to that reported in other French ICU despite the oversea location of our hospital. ESBL-PE carriage is frequently associated to ICU-AI, but, does not predict ESBL-PE as responsible germ of ICU-AI. However, antibiotic exposure is independent risk factor exposing to ICU-AI and to ICU-AI caused by ESBL-PE.

ESBL-PE are major concern worldwide. Surveillance networks reveal a predominance of K pneumoniae in Latin America (44%) and Asia Pacific regions (22%) with a lower incidence in Europe (13.3%) and in North America (7.5%) [16,17]. In addition, strains of E coli with ESBL type CTX-M producing in the community are widely disseminated throughout the world and are found endemic in Asia, South America and Europe[11].In Latin America, the incidence rate of *Enterobacteriacae* producing ESBL is among the highest in the world varyingfrom 45 to 51% for *K pneumoniae* and from 8.5 to 18% for *E coli* [18,19]. In addition, the ESBL producing can be worsened by the development of combined resistance mainly to fluoroquinolones and aminoglycosides in *Klebsiella pneumoniae* and *E coli* [20].

In ICU, patients have a significant risk to acquire ESBL-PE colonization. The acquisition rate varies from 3% to 21% according to the region of the study [34]. Previous hospitalization or antibiotic use and exposure to beta-lactams/beta-lactamase inhibitors and carbapenems during the ICU stay were independent risk factors for ICU-acquired colonization [34].

In a prospective study in a French 12-bed ICU, Repessé et al [21], report a rate of ESBL-PE colonization at admission at 13.2%. In this study, the incidence of ESBL-PE acquisition at 4.1%. SAPS II at admission was the only independent risk factor for ESBL acquisition.

Razazi et al [22], in a prospective study in ICU found that ESBL-PE carriage rate at admission was of 15 %, mostly of *E. coli* (62 %). Independent risk factors associated to ESBL-PE carriage at admission were transfer from another ICU, hospital admission in another country, surgery within the past year, prior neurologic disease, and prior administration of third generation cephalosporin (within 3-12 months before ICU admission). In this study, 13 % of patients staying for more than 5 days, acquired ESBL carriage in ICU, mostly with *E cloacae* (46 %) and *K pneumoniae* (36 %).

Overall, ESBL-PE carriage at admission to ICU is a major concern with an incidence rate reaching 30% in some studies [23–25]. Identifying carriers at admission is challenging because it allows to prevent cross transmission by using specific measures and to select appropriate antibiotic treatment in case of infection. Risk factors reported in most of studies are recent hospitalization and antibiotic exposure. These factors reflect the role of cross transmission and antibiotic pressure on the selection of bacterial resistance.
In French Guiana, the published literature on ESBL-PE carriage is focused only in the community [26–28]. Indeed, Woerther et al [28], in a prospective study in the Amerindian community of Trois-sauts found that the ESBL carriage prevalence, exclusively comprising *Escherichia coli*, was 8.0%. It mainly consisted of CTX-M type ESBL. No individual risk factor was identified in this study. However, the authors report the high level and the increase of antibiotic use in this community.

In our study, ESBL-PE carriage at admission was found in 9.3% of our patients. Exposure to antibiotics in the previous year was found in 11.8% of patients and hospitalization during the previous year was found in 21.6% of patients. The main ESBL-PE isolated in the screening tests was *E coli*. During hospitalization in ICU, ESBL-PE carriage was recorded in 13.5% of patients non ESBL-PE carriers at admission. The main ESBL-PE isolated in the screening tests was *K pneumoniae*. Colonization index during the study period shows high prevalence of ESBL-PE carriage (35% in the average) with a pic at the second year of the study (2014; up to 65%). Colonization index was linked to ESBL-PE carriage acquisition in ICU because of cross transmission. Indeed, ESBL-PE carriage can be linked to the colonization pressure on the ward [9,29] and include the transmission of ESBL-PE from colonized to non-colonized patients. But, it can be related to acquisition through the endogenous route which represents the situation where bacteria are already present in the host at undetectable levels and reach detectable levels under antibiotic pressure [24,25,30–37]. For this, antibiotics management in the community and in the hospital is challenging with prudent use of major antibiotics to prevent their impact on the microbial ecology. In our study, we did not studied factors associated to ESBL-PE acquisition. We think that colonization pressure and antibiotic use are both responsible of the transmissibility and the selection of ESBL-PE.
Our results are in accordance with data from Europe and North-America and shows a less important level of ESBL-PE carriage than expected because of the South American location of our hospital.

The relationship between ESBL-PE carriage and subsequent infection is controversial. In some studies, ESBL-PE carriage was reported to be associated to a higher risk of subsequent infection in ICU patients with a higher rate of ESBL-PE infection among colonized than in non-colonized patients [23]. However, other recent studies found that the incidence of ICU-AI caused by ESBL-PE is relatively weak in carriers (10 to 25%) [8,38–42]. Razazi et al. [1], in a prospective study in a medical ICU found that in carriers, ESBL-PE caused only 10 and 27 % of first and second episodes of ICU-acquired infections, respectively. Barbier et al. [8]in an inception cohort study from the French prospective multicenter OUTCOMEREA database found that among the 318 enrolled ESBLE carriers, only 7% developed infections caused by ESBL-EP. Carbapenem exposure within the preceding 3 days was the sole independent predictor of ESBL-PE infection. they conclude that ESBL-PE related infections are scarce and hard to predict. Lindblom et al. [42], subsequent ESBL-PE related infections in previously colonized patients were rare. In addition, switching from universal to targeted active surveillance cultures had no impact on the incidence of ICU-acquired ESBL-E infections [25,26]. All these findings led some authors to suspect that screening for ESBL-PE carriage is powerless in predicting subsequent infection, and it can be a driver to an over use of carbapenems [43].

Thus, recent studies have challenged the benefit of active surveillance cultures to detect intestinal carriage of ESBL-PE in controlling the spread of ESBL-E in ICUs with high compliance to standard hygiene precautions and no ongoing outbreak of ESBL-PE. In addition, given their debated performance to positively predict which patients are at risk of ESBL-PE infections, active surveillance cultures results seem of limited value to rationalize the empirical use of carbapenems in the ICU.

In our study, 367 patients were ESBL-PE carriers, and 37.3% of them developed ICU-AI. The causative germ was an ESBL-PE in 28.4% of cases. Thus, ESBL-PE carriage showed a weak value to predict a subsequent ICU-AI. However, factors associated to ICU-AI in ESBL-PE carriers and those associated to ESBL-PE ICU-AI showed an important role of antibiotic exposure mainly to imipenem. Our results are concordant with those reported in the recent literature. They show a high level of ESBL-PE carriage, but, a little impact on subsequent infections. Indeed, ESBL-PE caused ICU-AI in only 19% and 16.7% of the first and second episode in carriers. In addition, the carriage of ESBL-PE showed a little value to predict subsequent ICU-AI with only 61.9% sensibility, 56.8% specificity, 28.5% Positive Predictive Value, and 84.3% Negative Predictive Value.

Carbapenems are widely used antibiotics resulting in increased resistance among the *Enterobactericae*, with limited therapeutic alternatives [44,45]. In our hospital, Carbapenems use is under close monitoring to survey inappropriate prescriptions. A postprescription stewardship is carried out since 2015 with a weekly evaluation of all carbapenem prescriptions regarding the appropriateness of prescriptions, review of prescriptions at 48-72 h according to the microbiological results, wider use of alternatives to carbapenems when allowed, and high attention to the duration of carbapenem cure [46]. This management allowed a significant reduction in carbapenems use from 8.3 ± 3.4 to 5.3 ± 2.3 DDD/1000 patient-days. In our experience, ESBL-PE carriage is a strong driver of empirical prescription of carbapenems in patients with severe infection. In this step, a broad spectrum antibiotic is warranted because of the high risk of initial inappropriateness and its impact on the outcome of patients [47]. But, after determination of ESBL-PE susceptibility pattern, reevaluation of the antibiotic prescription is needed especially that prescription alternatives can be achievable in daily practice.

Son et al. [48] compared the treatment effectiveness of carbapenems and alternative antibiotics in patients with ESBL-PE. The findings from this meta-analysis showed that overall mortality did not differ when carbapenems were compared with non-B lactams/B lactams Inhibitors (BL/BLIs), with cephalosporins or with BL/BLIs in empirical therapy, or when carbapenems were compared with quinolones in definitive therapy. Other studies had evaluated the effectiveness of non-carbapenem alternatives to treat ESBL-PE related bacteremia. No association between empirical therapy with BL/BLIs combination and increased mortality was found [49]. A similar result was found in a systematic review and meta-analysis including 21 articles and 1584 patients [50]. By contrast, increased risk of mortality in blood stream infections caused by ESBL-PE treated with non-carbapenem alternatives was also reported [51] .

Our study has two limitations, first this is a monocentric study. However, our unit is the only ICU unit of French Guiana. For this reason, the overview of the local situation is almost exhaustive. The second limitation is that bacterial identification was only phenotypic without information on the genotypic typing of ESBL. But, in the best of our knowledge, this study is the first one reporting ESBL-PE carriage and infections in the Guiana shild and in the French Departments of America. Further studies are needed to explore genotypic typing of ESBL and to search for decision-making tools for a relevant management of carbapenems.

In conclusion, in a practice point of view, and according to our results and to the literature reports, prescribing carbapenems in patients carrying ESBL-PE is not pertinent in 80% of cases. In the absence of routine clinical predictors of resistance, ESBL-PE carriage act as a strong driver of carbapenems use and then, of resistance trigger. Antibiotic reevaluation at 24-72 hours and at 5 days are necessary to revise prescription according to microbiological data. Even if recent data are concordant to stop screening for ESBL-PE in low endemic ICU, we raise the question of the pertinence to stop screening also in high endemic ICU.

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APPENDIX

Appendix A: Demographic and clinical characteristics of ESBL-PE carriers hospitalized for more than 48 hours, with and without ICU-AI

	ICU-AI (+)		ICU-AI (-)		
Variable	**Nb**	**Result**	**Nb**	**Result**	**p**
Age (years)	137	50 [35-63]	230	47 [31-63]	0.036
Male gender	137	96 (70.1%)	230	126 (54.8%)	0.004
BMI	115	25.4 [22.4-31]	187	25 [21.4-29.9]	0.954
SAPS II	137	49 [40-64]	230	45 [28-63]	0.024
Comorbidities	137	72 (52.6%)	230	119 (51.7%)	0.88
Arterial hypertension	137	49 (35.8%)	230	80 (34.8%)	0.849
Diabetes mellitus	137	24 (17.5%)	230	41 (17.8%)	0.94
Cancer	137	8 (5.8%)	230	27 (11.7%)	0.233
Immunodeficiency	137	26 (19%)	230	88 (38.3%)	0.098
Chronic renal failure	137	10 (7.3%)	230	22 (9.6%)	0.457
Chronic respiratory failure	137	2 (1.5%)	230	3 (1.3%)	0.901
Sickle cell disease	137	5 (3.6%)	230	7 (3%)	0.752
Type of admission	137	179 (130.7%)	230		0.348
Medical	137	98 (71.5%)	230	156 (67.8%)	0.457
Elective surgery	137	3 (2.2%)	230	12 (5.2%)	0.157
Emergent surgery	137	36 (26.3%)	230	62 (27%)	0.887
Traumatic	137	40 (29.2%)	230	33 (14.3%)	0.001
ATB during previous year	137	22 (16.1%)	230	49 (21.3%)	0.525
In the last 3 months	137	14 (10.2%)	230	27 (11.7%)	0.655
In the last 3 to 6 months	137	5 (3.6%)	230	11 (4.8%)	0.607
In the last 6 to 12 months	137	3 (2.2%)	230	11 (4.8%)	0.21
Hospitalization during previous year	137	38 (27.7%)	230	82 (35.7%)	0.345
In the last 3 months	137	17 (12.4%)	230	42 (18.3%)	0.14
In the last 3 to 6 months	137	6 (4.4%)	230	15 (6.5%)	0.393
In the last 6 to 12 months	137	15 (10.9%)	230	25 (10.9%)	0.981
Direct admission from ED	137	106 (77.4%)	230	139 (60.4)	0.001
Organ failure at admission	137	3 [2-3]	230	2 [1-3]	0.007
Hemodynamic	137	84 (61.3%)	230	100 (43.5%)	0.001
Respiratory	137	99 (72.3%)	230	131 (57%)	0.003
Neurologic	137	83 (60.6%)	230	100 (43.5%)	0.002
Kidney	137	47 (34.3%)	230	79 (34.3%)	0.994
Liver	137	26 (19%)	230	32 (13.9%)	0.198
Hematologic	137	29 (21.2%)	230	57 (24.8%)	0.429

Active infection at admission	137	81 (59.1%)	230	147 (63.9%)	0.36
Bacteraemia	81	13 (16%)	147	28 (19%)	0.573
Antibiotics at admission	137	115 (83.9%)	230	179 (77.8%)	0.156
Amoxicillin clavulanate	137	43 (31.4%)	230	36 (15.7%)	0.00
Aminoglycosides	137	39 (28.5%)	230	90 (39.1%)	0.038
Piperacillin-Tazobactam	137	33 (24.1%)	230	62 (27%)	0.544
3rd generation cephalosporins	137	21 (15.3%)	230	43 (18.7%)	0.411
Imipenem	137	9 (6.6%)	230	27 (11.7%)	0.107
Fluoroquinolones	137	13 (9.5%)	230	23 (10%)	0.874
Metronidazole	137	2 (1.5%)	230	9 (3.9%)	0.182
Mechanical ventilation	137	124 (90.5%)	230	149 (64.8%)	0.000
Time from admission to MV	124	0 [0-0]	149	0 [0-0]	0.812
Overall duration of MV	124	4400	149	1810	0.163
MV more than 48 hours	124	123 (99.2%)	149	109 (73.2%)	0.000
Duration of MV without VAP	124	2526	149	1810	0.000
Tracheostomy	137	28 (20.4%)	230	5 (2%)	0.000
Renal replacement therapy	137	27 (19.7%)	230	28 (12.2%)	0.05
Time from admission to RRT	27	1 [0-4]	28	0 [0-1]	
Central venous catheter	137	131 (95.6%)	230	167 (72.6%)	0.000
Overall duration of CVC	131	4409	167	2516	0.000
Duration of CVC without infection	131	3934	167	2516	0.000
Arterial catheter	137	127 (92.7%)	230	150 (65.2%)	0.000
Overall duration of AC	127	2405	150	1346	0.000
Duration of AC without infection	127	2308	150	1346	0.000
ATB exposure during hospitalization					
Amoxicillin clavulanate	137	41 (29.9%)	230	37 (16.1%)	0.002
Aminoglycosides	137	97 (70.8%)	230	98 (42.6%)	0.000
Piperacillin-Tazobactam	137	69 (50.4%)	230	73 (31.7%)	0.000
3rd generation cephalosporins	137	59 (43.1%)	230	52 (22.6%)	0.000
Imipenem	137	54 (39.4%)	230	34 (14.8%)	0.000
Fluoroquinolones	137	24 (17.5%)	230	30 (13%)	0.242
Metronidazole	137	3 (2.2%)	230	13 (5.7%)	0.116
ESBL-PE carriage	137	137 (100%)	230	230 (100%)	
ESBL-PE carriage at admission	137	33 (24.1%)	230	126 (54.8%)	0.000
Colonisation Pressure	137	264 [59-617]	230	30.6 [0-224]	0.000
Time from admission to ESBL-PE	137	10 [3-17]	230	1 [0-7]	0.000

ATB exposure prior to ICU-AI	137		0		
Amoxicillin clavulanate	137	41 (29.9%)	0	0 (%)	-
Aminoglycosides	137	56 (40.9%)	0	0 (%)	-
Piperacillin-Tazobactam	137	37 (27%)	0	0 (%)	-
3rd generation cephalosporins	137	32 (23.4%)	0	0 (%)	-
Imipenem	137	28 (20.4%)	0	0 (%)	-
Fluoroquinolones	137	10 (7.3%)	0	0 (%)	-
Metronidazole	137	1 (0.7%)	0	0 (%)	-
ICU-AI	137	137 (100%)	230	0 (%)	
Ventilator associated pneumonia	124	65 (47.4%)	230	0 (%)	-
Density-incidence of VAP (/1000 days MV)	124	25.7	230		-
Bacteraemia	137	91 (66.4%)	230	0 (%)	-
CVC related infection (CVC-RI)	131	45 (34.4%)	167	0 (0%)	0.000
Density-incidence of CVC-RI (/1000 days CVC)	131	11.4			-
AC related infection (AC-RI)	127	19 (15%)	150	0 (0%)	0.000
Density-incidence of AC-RI (/1000 days AC)	127	8.2			-
Time from admission to ICU-AI	137	9 [5-16]	0		-
ICU-AI Caused by ESBL-PE	137	39 (28.5%)	0	0 (%)	-
Time from admission to ESBL-PE	39	14 [9-22]	0		-
Outcome					
ICU LOS (days)	137	50 [36-63]	230	9 [4-18]	0.000
Death	137	32 (23.4%)	230	54 (23.5%)	0.979
Death in the first 24 hours	137	0 (0%)	54	2 (3.7%)	0.271

Appendix B: Demographic and clinical characteristics of ESBL-PE carriers' patients with ICU acquired infection according to ESBL producing of the causative Enterobacteriaceae.

	ESBL-PE (+)		ESBL-PE (-)		
Variable	**Nb**	**Result**	**Nb**	**Result**	**p**
Age (years)	39	52 [42-66]	98	49 [35-62]	0.633
Male gender	39	25 (64.1%)	98	71 (72.4%)	0.336
BMI	35	28 [24.4-35.5]	80	24.4 [21.9-30]	0.23
SAPS II	39	57 [41.5-74]	98	49 [39.3-59]	0.338
Comorbidities	39	21 (53.8%)	98	51 (52%)	0.849
Arterial hypertension	39	12 (30.8%)	98	37 (37.8%)	0.441
Diabetes mellitus	39	10 (25.6%)	98	14 (14.3%)	0.115
Cancer	39	5 (12.8%)	98	3 (3.1%)	0.028
Immunodeficiency	39	11 (28.2%)	98	15 (15.3%)	0.533
Chronic renal failure	39	6 (15.4%)	98	4 (4.1%)	0.022
Chronic respiratory failure	39	1 (1.6%)	98	2 (2%)	0.369
Sickle cell disease	39	1 (2.6%)	98	4 (4.1%)	0.669
Type of admission	39	47 (120.5%)	98		0.306
Medical	39	31 (79.5%)	98	67 (68.4%)	0.193
Elective surgery	39	0 (0%)	98	3 (3.1%)	0.269
Emergent surgery	39	8 (20.5%)	98	28 (28.6%)	0.334
Traumatic	39	4 (10.3%)	98	36 (36.7%)	0.002
ATB during previous year	39	11 (28.2%)	98	11 (11.2%)	0.008
In the last 3 months	39	7 (17.9%)	98	7 (7.1%)	0.06
In the last 3 to 6 months	39	1 (2.6%)	98	4 (4.1%)	0.669
In the last 6 to 12 months	39	3 (7.7%)	98	0 (0%)	0.005
Admission during previous year	39	108 (276.9%)	98	23 (23.5%)	0.308
In the last 3 months	39	6 (15.4%)	98	11 (11.2%)	0.505
In the last 3 to 6 months	39	3 (7.7%)	98	3 (3.1%)	0.232
In the last 6 to 12 months	39	6 (15.4%)	98	9 (9.2%)	0.294
Direct admission from ED	39	28 (71.8%)	98	78 (79.6%)	0.325
Organ failure at admission	39	3 [2-4]	98	2.5 [2-3]	0.035
Hemodynamic	39	30 (76.9%)	98	54 (55.1%)	0.018
Respiratory	39	32 (82.1%)	98	67 (68.4%)	0.106
Neurologic	39	23 (59%)	98	60 (61.2%)	0.808
Kidney	39	18 (46.2%)	98	29 (29.6%)	0.065
Liver	39	10 (25.6%)	98	16 (16.3%)	0.21
Hematologic	39	13 (33.3%)	98	16 (16.3%)	0.028

Active infection at admission	39	27 (69.2%)	98	54 (55.1%)	0.129
Bacteraemia	27	5 (18.5%)	54	8 (14.8%)	
Antibiotics at admission	39	37 (94.9%)	98	78 (79.6%)	0.028
Amoxicillin clavulanate	39	8 (20.5%)	98	35 (35.7%)	0.084
Aminoglycosides	39	16 (41%)	98	23 (23.5%)	0.04
Piperacillin-Tazobactam	39	15 (38.5%)	98	18 (18.4%)	0.013
3rd generation cephalosporins	39	7 (17.9%)	98	14 (14.3%)	0.591
Imipenem	39	4 (10.3%)	98	5 (5.1%)	0.272
Fluoroquinolones	39	6 (15.4%)	98	7 (7.1%)	0.137
Metronidazole	39	1 (1.6%)	98	2 (2%)	0.369
Mechanical ventilation	39	38 (97.4%)	98	86 (87.8%)	0.081
Time from admission to MV	38	0 [0-0]	86	0 [0-0]	0.414
Overall duration of MV	38	1479	86	2921	
MV more than 48 hours	38	38 (100%)	86	85 (98.8%)	0.505
Duration of MV without VAP	38	929	86	1597	
Tracheostomy	39	9 (23%)	19	19 (100%)	0.629
Renal replacement therapy	39	13 (33.3%)	98	14 (14.3%)	0.011
Time from admission to RRT	13	1 [0-7]	14	0 [0-2]	
Central venous catheter	39	37 (94.9%)	98	94 (95.9%)	0.787
Overall duration of CVC	37	1492	94	2917	0.204
Duration of CVC without infection	37	1248	94	2686	0.255
Arterial catheter	39	37 (94.9%)	98	90 (91.8%)	0.538
Overall duration of AC	37	852	90	1553	0.005
Duration of AC without infection	37	820	90	1488	0.009
ATB exposure during hospitalization					
Amoxicillin clavulanate	39	6 (15.4%)	98	35 (35.7%)	0.019
Aminoglycosides	39	32 (82.1%)	98	65 (66.3%)	0.068
Piperacillin-Tazobactam	39	18 (46.2%)	98	51 (52%)	0.534
3rd generation cephalosporins	39	14 (35.9%)	98	45 (45.9%)	0.285
Imipenem	39	28 (71.8%)	98	26 (26.5%)	0.000
Fluoroquinolones	39	7 (17.9%)	98	17 (17.3%)	0.933
Metronidazole	39	1 (1.6%)	98	3 (3.1%)	0.269
ESBL-PE carriage	39	39 (100%)	98	98 (100%)	
ESBL-PE carriage at admission	39	15 (38.5%)	98	18 (18.4%)	0.013
Colonisation Pressure	39	97.4 [0-225.4]	98	361.5 [107-701]	0.000
Time from admission to ESBL-PE carriage (days)	39	4 [1-9]	98	13 [5-19]	0.036

ATB exposure prior to ICU-AI	39	39 (100%)	98	74 (75.5%)	0.01
Amoxicillin clavulanate	39	6 (15.4%)	98	35 (35.7%)	0.019
Aminoglycosides	39	27 (69.2%)	98	29 (29.6%)	0
Piperacillin-Tazobactam	39	17 (43.6%)	98	20 (20.4%)	0.006
3rd generation cephalosporins	39	13 (33.3%)	98	19 (19.4%)	0.082
Imipenem	39	15 (38.5%)	98	13 (13.3%)	0.001
Fluoroquinolones	39	0 (0%)	98	10 (10.2%)	0.038
Metronidazole	39	0 (0%)	98	1 (1%)	0.527
ICU-AI	39	39 (100%)	98	98 (100%)	
Ventilator associated pneumonia	39	17 (43.6%)	98	48 (48.9%)	
Density-incidence of VAP (/1000 days MV)	39	18.2	98	30.1	
Bacteraemia	31	31 (100%)	60	60 (100%)	
CVC related infection (CVC-RI)	37	18 (48.6%)	94	27 (28.7%)	0.031
Density-incidence of CVC-RI (/1000 days CVC)	37	14.4	94	10.1	
AC related infection (AC-RI)	37	5 (13.5%)	90	14 (15.6%)	0.769
Density-incidence of AC-RI (/1000 days AC)		6.1		9.4	
Time from admission to ICU-AI	39	11 [7.5-17.5]	98	9 [5-15]	0.802
ICU-AI Caused by ESBL-PE	39	39 (100%)	98	0 (0%)	
Time from admission to ESBL-PE ICU-AI (days)	39	14 [9-22]	0	11 [7-19]	0.36
Outcome					
ICU LOS (days)	39	37 [24-63]	98	32 [20-52]	0.784
Death	39	11 (28.2%)	98	21 (21.4%)	0.398

UFR SCIENCES MEDICALES HYACINTHE BASTARAUD

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.

COURT THIBAULT

SUJET DE LA THESE :
Quantifying Carriage of Extended-Spectrum Beta-Lactamase-Producing Enterobacteriaceae and subsequent ICU acquired infection in French Guiana.

THESE : MEDECINE **Qualification : Médecine Spécialisée**

ANNEE :2018
NUMERO D'IDENTIFICATION : 2018ANTI0369
MOTS CLEFS : INTENSIVE CARE UNIT, ACQUIRED INFECTION, SURVEILLANCE, INCIDENCE, EXTENDED-SPECTRUM B-LACTAMASE-PRODUCING *ENTEROBACTERIACEAE*

Introduction
La colonisation à entérobactéries productrices de B-lactamase à Spectre Etendu (PE-BLSE) en réanimation est responsable d'une surmortalité et d'une sur morbidité. Le but de notre travail était de quantifier le portage de PE-BLSE en réanimation et à déterminer son impact sur les infections acquises en réanimation (IAR).
Matériels et méthodes
Notre étude est prospective observationnelle non interventionnelle. Il a été mené sur une période de 5 ans (janvier 2013 à décembre 2017) dans le service de réanimation polyvalente du Centre Hospitalier de Cayenne.
Résultats
Au cours de la période d'étude, 1698 patients ont été admis dans notre service. L'âge médian de nos patients était de 44 ans [28-60]. Une ou plusieurs comorbidités ont été enregistrées chez 45,6% des patients. Une immunodépression a été enregistrée chez 30,8% des patients.
Cinquante-neuf patients (9,3%) étaient porteurs de ES-BLSE à l'admission en réanimation et 208 patients ont acquis le portage pendant le séjour (13,5% des non-porteurs à l'admission). Parmi les 367 patients porteurs de ES-BLSE, 137 patients (37,3%) ont développé une IAR. Après analyse par régression logistique, les facteurs indépendants associés à la survenue d'une IAR étaient: patient traumatisé (p: 0,029; OR: 2,5 [1,1 - 5,7]), Ventilation Mécanique > 48 heures (p: 0,006; OR: 17,5 [2,2 à 136,7]), trachéotomie (p : 0,006; OR: 4,6 [1,5 -13,9]), épuration extra-rénale (p: 0,030, OR: 2,5 [1,1 - 5,9]), cathétérisme artériel (p: 0,033, OR: 4,1 [1,1 -14,8]), exposition à : AMX-Clav (p: 0,014; OR: 2,8 [1,2 -6,3]), à PIP-TAZ (p: 0,007; OR: 2,5 [1,3 -4,8]), aux C3G (p: 0,000; OR: 3,6 [1,8 à 7,3]) et à l'Imipenème (p: 0,000; OR: 6,1 [2,8 -13,2]) au cours de l'hospitalisation. L'IAR chez les patients porteurs d'ES-BLSE a été causée par une ES-BLSE dans 39 cas (28,4%). Les facteurs associés à l'IAR causée par une ES-BLSE chez les porteurs d'ES-BLSE étaient l'admission pour cause traumatique (p: 0,001; OR: 0,1 [0 -0,5]), défaillance hémodynamique à l'admission (p: 0,005; OR: 4,2 [1,5 -11,4]) et exposition à l'Imipenème avant l'infection (p: 0,025; OR: 3,2 [1,2 -8,9]). La valeur prédictive positive du portage d'ES-BLSE pour prédire qu'une IAR est causée par une ES-BLSE était de 28,5% et la valeur prédictive négative de 84,3%.
Conclusion :
Le portage d'ES-BLSE est souvent associé à la survenue d'IAR, mais ne prévoit pas que l'ES-BLSE en soient responsable. L'exposition aux antibiotiques notamment aux carbapénèmes est un facteur de risque indépendant de survenue d'IAR et de survenue d'IAR causée par une ES-BLSE.

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