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Broad-Spectrum-Beta Lactamase Secreting Enterobacteria Isolated from Healthcare Associated Infections at the Tsaralalana Mother University Hospital Center

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ABSTRACT

Healthcare -associated infectious (HAIs) represent a major threat to the quality of peadiatric care, especially when they are associated with multi-resistants germs. The main objective of this study was to determine the incidence of HAIs linked to EBLSE and the factors associated with their occurrence at the Tsaralalana Mother University Hospital Center (CHUMET.) A retrospective case-control study was carried-out over 5-year period. All patients suspected of having a bacterial infection from a 48th hour of admission, with a positive bacteriolgical examination for EBLSE were included. Controls were those with the same criteria but whose bacteriolgical examination was negative. Matching was based on age, period and hospital ward, with 1:2 ratio. Of 218 hospitalised patients aged <15 yaers with a documented with HCAI, 129 were due to EBLSE, with an incidence of 0.9%. A total of 53 cases were included in the study the media age of the patients was 2 months, with a

predominance of neonates (n=34, 64,1%). *Enterobacter sp* et *Klebsiella sp* were most frequently detected. Low birth weight [OR=3,05; CI 1,19-8,01; p=0,01], gastric tube feeding [0R=6,56, CI 2,19-19,62, p=0,0002] and oxygen therapy [OR= 9,21; CI 2,95-39,53, p=0,00004] were the risk factors identified. Monitoring, application and evaluation of control measures and IPC activities within pediatric hospital establishments constitue the cornerstone of the fight against HAIs and quality of care.

Keywords: Enterobacteriaceae, Extended Spectrum Beta-lactamase, Healthcare-associated infections.

INTRODUCTION

Healthcare-associated infections (HAIs) are defined as infections that are neither present nor incubating at the time of a patient's admission and are acquired during or after the course of medical care in a healthcare facility [1]. They represent a global health concern among hospitalized patients. HAIs can be severe due to their serious prognosis, potential mortality, and increased healthcare costs. The pediatric population, considered a high-risk group due to the immaturity of their immune system, is also affected [2]. Various microorganisms can be involved, particularly bacteria, which can be formidable due to their resistance mechanisms against commonly used antibiotics. An increasing number of studies report the emergence of extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae (ESBL-E) among pediatric patients. These enzymes, produced by Enterobacteriaceae, can hydrolyze third-generation cephalosporins (C3G), rendering them inactive [1]. Moreover, Enterobacteriaceae are commensal organisms of the intestinal flora and can easily persist in the environment when hygiene practices are inadequate. ESBL-E infections can be severe, leading to prolonged hospital stays and increased healthcare costs [2-4].

The primary objective of this study was to determine the incidence of ESBL-E-associated HAIs and the factors associated with their occurrence in pediatric patients. Secondarily, the study also examined the species of ESBL-producing Enterobacteriaceae and their associated resistance profiles against other commonly prescribed antibiotic families.

METHODS

This was a retrospective, monocentric case-control study conducted at the Tsaralalàna Mother-Child University Hospital Center (CHUMET), a referral pediatric hospital in Madagascar's capital, caring for children under 15 years of age. The study spanned five years, from January 2018 to December 2022. All hospitalized children with a length of stay >48 hours were included.

"Cases" were defined as patients presenting clinical and/or biological signs suggestive of a bacterial infection from the 48th hour of admission onward, with a clinical sample testing positive for ESBL-E. "Controls" were defined as patients who did not develop an infection from the 48th hour of hospitalization until discharge or had clinical and/or biological signs of a bacterial infection but tested negative for ESBL-E. Matching was performed based on age, hospitalization period, and hospital service, with a case-to-control ratio of 1:2. Patients with a history of hospitalization in the past 12 months were excluded, as well as those hospitalized for more than 48 hours but with a positive bacteriological test for non-Enterobacteriaceae

pathogens or Enterobacteriaceae without an ESBL phenotype. Patients with missing or incomplete clinical records were also excluded.

Laboratory confirmation of ESBL-E at CHUMET was based on microscopy, oxidase testing, and API 20E (Biomérieux, France). Antibiotic susceptibility testing was performed and interpreted according to the standards of the French and European Society of Microbiology's Antibiogram Committee (CA-SFM/EUCAST). ESBL production was confirmed by the synergy test.

Demographic variables studied included gender, age group, and hospital service. Parameters indicative of probable HAIs after 48 hours of hospitalization (axillary temperature >38°C, clinical deterioration assessed by the Blantyre or Glasgow score, skin mottling, C-reactive protein (CRP) >6 mg/L) and factors associated with ESBL-E HAIs (birth weight, gestational age, prior or on-admission antibiotic therapy, and invasive procedures) were analyzed. Microbiological data included the bacterial species isolated and their resistance profiles to other therapeutic alternative antibiotics: aminoglycosides (gentamicin and amikacin), fluoroquinolones (ciprofloxacin), and phenicols (chloramphenicol).

Data were collected from hospitalization registers, laboratory records, and patient files using pre-established and pre-tested data sheets. Data entry and analysis were performed using Epi-Info v7.0 software. Quantitative data were expressed as mean and standard deviation, while qualitative data were presented as frequency and percentage. Odds ratios (OR) and their 95% confidence intervals (95% CI) were used to assess associations between risk factors and ESBL-E HAIs. An OR >1 with a 95% CI not including 1 and a p-value <0.05 was considered a risk factor for ESBL-E HAI.

The retrospective nature of the study limited objective analysis of infection prevention and control practices among healthcare personnel, such as hand hygiene, as well as intrinsic factors related to ESBL-E carriage at admission. The high cost of microbiological analyses for colonization screening and limited resources were also constraints. Ethical approval was obtained from the relevant authorities and the hospital director.

RESULTS

Among the 13,909 children aged ≤15 years hospitalized at CHUMET during the study period, 218 (1.5%) had a documented bacterial healthcare-associated infection (HAI). Among these cases, 129 (59.1%) were due to extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, representing an incidence of 0.9%.

Seventy-six patients (n=76) were excluded due to missing or incomplete medical records. In total, 53 cases of ESBL-producing Enterobacteriaceae HAIs were included in the study.

The age of patients with ESBL-producing Enterobacteriaceae HAI ranged from 0 days to 6 years, with a median age of 2 months. The majority of patients were newborns (n=34, 64.1%) (Table I) and originated from the neonatal unit in 45.2% (n=24) of cases (Figure 1).

After 48 hours of hospitalization, fever was the predominant clinical sign indicating the likelihood of an HAI (79.2%, n=42), and elevated C-reactive protein (CRP) levels were found in 81.1% (n=43) of cases (Table II).

Table I : Age range of patients with EBLSE HAIs

Age range	Number (N=53)	Percentage (%)
[00 - 30 days [	34	64,1
[30 jours - 6 months [	7	13,2
[06 - 12 months [	4	7,5
[12 - 24 months [	2	3,8
[24 - 59 months [	5	9,4
≥ 59 months	1	1,9

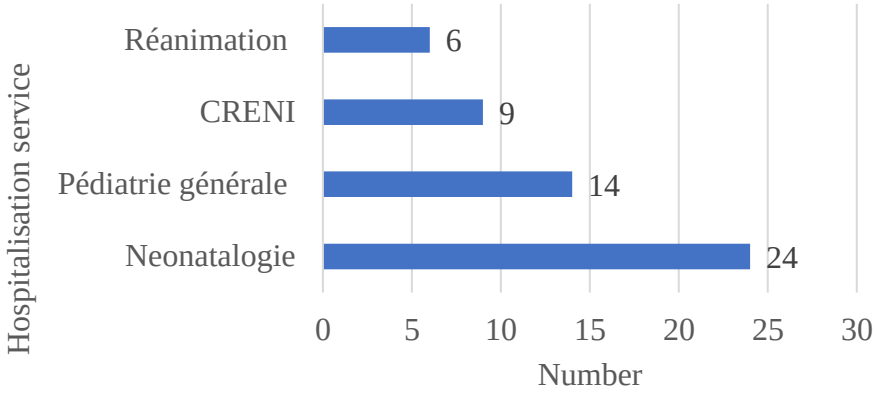

Figure 1: Distribution of EBLSE HCAI cases by hospital ward
CRENI: Centre de Récupération Nutritionnelle Intensive (Intensive Nutritional Recovery Center)

Table II: Clinico-biological parameters pointing to HCAI after the 48th hour of hospitalization

Parameters	Catégory	Number (n=53)	Percentage (%)
Clinical			
Fever (Axillary T° > 38°C)	**Yes**	**42**	**79,2**
	No	11	20,7
Clinical degradation	Yes	20	37,7
	No	33	62,2
Skin mottling	Yes	4	7,5
	No	49	92,4
Biological			
High CRP	**Yes**	**43**	**81,1**
	No	10	18,9

Among the 53 included patients, 92.4% (n=49) received antibiotic therapy upon admission, of whom 93.8% were treated with third-generation cephalosporins (C3G) (n=46), and 6.2% received aminopenicillins or penicillins combined with beta-lactamase inhibitors (BLI). An antibiotic treatment duration exceeding 5 days was observed in 50.9% of cases (n=27).

In this study, newborns with a low birth weight (<2500 g) had a threefold higher risk of developing ESBL-producing Enterobacteriaceae HAIs compared to those with a birth weight above 2500 g [OR: 3.05, 95% CI: 1.19-8.01], p = 0.01. Regarding invasive procedures, gastric tube feeding and oxygen therapy increased the risk of ESBL- producing Enterobacteriaceae HAI six- and ninefold, respectively, compared to patients who did not receive these interventions

during hospitalization [OR: 6.56; 95% CI: 2.19-19.62; p = 0.0002], [OR: 9.21; 95% CI: 2.95-39.53; p = 0.00004] (Table III).

Table III: Determinants of EBLSE HAIs

	Case n=53	**Control n=106**	**Total**	**OR**	**IC 95%**	***p-value***
Prematurity						
Extremely preterm	5	6	11	1,72	[0,44-6,64]	0,42
Moderate preterm	9	22	31	0,84	[0,31-2,31]	0,74
Very extremely preterm	2	1	3	4,14	[0,34-49,65]	0,23
Full term	14	29	43	-	-	-
Birth weight						
Low weight	15	16	31	**3,05**	**[1,19-8,01]**	**0,01**
Normal weight	13	43	56			
Antibiotics at admission						
Yes	49	97	146	1,13	[0,33-4,43]	0,55
No	4	9	13			
C3G* at admission						
Yes	46	82	128	1.92	[0.76, 4.80]	0.15
No	7	24	31			
Venous access						
Yes	51	100	151	1,52	[0,31-11,32]	0,71
No	2	6	8			
Peripheral catheter						
Yes	35	53	88	1,9	[0,96-3,83]	0,06
No	18	52	70			
Gastric feeding						
Oui	49	69	118	**6,56**	[2,19-19,62]	2
Non	4	37	41			
Oxygénotherapy						
Oui	50	68	118	**9,21**	[2,95-39,53]	4
Non	3	38	41			

*C3G: *Cephalosporin third generation*

All ESBL-producing Enterobacteriaceae were isolated from blood cultures. Enterobacter spp. and Klebsiella spp. were the most frequently isolated Enterobacteriaceae, accounting for 62.2% (n=33) and 30.1% (n=16) of cases, respectively (Figure 2).

Table IV presents the resistance profile of ESBL-producing Enterobacteriaceae to the most commonly prescribed antibiotic families. All strains remained susceptible to amikacin and imipenem.

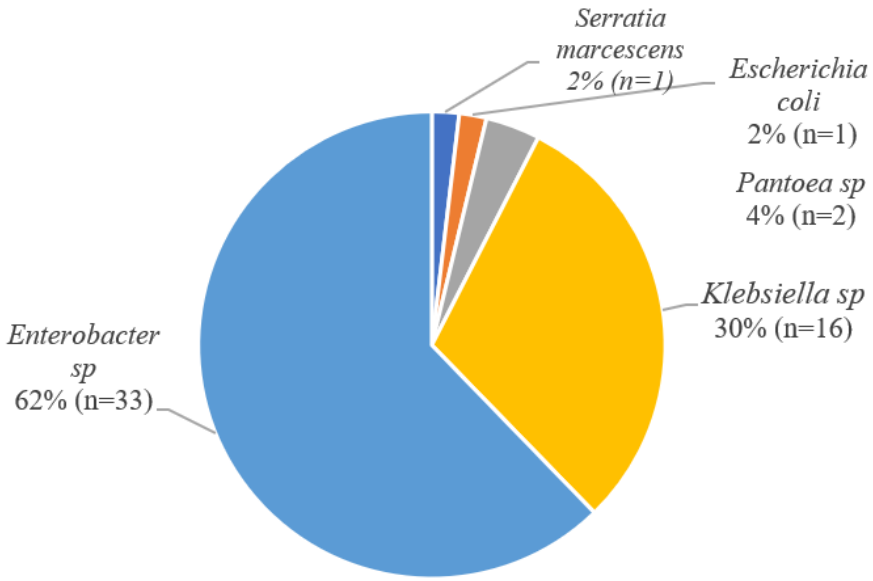

Figure 2: Extended-spectrum beta-lactamase-producing Enterobacteriaceae species isolated in healthcare-associated infections (HAIs)

Table IV: Resistance profile to other classes of antibiotics for ESBL-producing Enterobacteriaceae isolated in healthcare-associated infections (HAIs)

Antibiotics families	Resistance	Number n=53 (%)
Gentamicine	**Yes**	**46 (86,8)**
	No	7 (13,2)
Amikacine	Yes	0
	No	53 (100)
Ciprofloxacine	**Yes**	**42 (79,2)**
	No	11 (20,7)
Chloramphénicol	**Yes**	**26 (49,0)**
	No	27 (50,9)

DISCUSSIONS

Worldwide, it is estimated that hundreds of millions of patients each year, both in developed and low-income countries, are affected by healthcare-associated infections (HAIs). The magnitude of this infection in resource-limited countries remains underestimated and uncertain due to the lack of epidemiological data. Infections caused by ESBL-producing Enterobacteriaceae are becoming a major challenge in the clinical management of HAIs in hospitalized patients. The pediatric population is not spared from this threat.

Therapeutic options for these infections are limited, as fewer antibiotics are approved for use in children [5]. During this study, the incidence of laboratory-documented HAIs at CHUMET was 1.5%. In several reports, the incidence of HAIs varies between 3.9% and 57.7%, representing 40% of neonatal deaths in developing countries [6]. The HAI rate in a hospital is an indicator of the quality of care provided, particularly in terms of hospital hygiene, encompassing infection prevention and control. Since the study period coincided with the COVID-19 pandemic, during which hygiene measures were reinforced beyond usual practices, including restrictions on patient visits, this could explain the overall lower incidence observed.

An incidence of ESBL-producing Enterobacteriaceae HAIs of 0.9% was found, which is close to a study conducted in Poland on ESBL infections in hospitalized children, where the authors reported an incidence of 0.5% [7]. A literature review on infections associated with ESBL-producing Enterobacteriaceae in different countries worldwide identified a range of 28–40% in resource-limited countries and 8–12% in wealthy nations [8]. These variations can be explained by differences in clinical practices and resource utilization, such as inadequate healthcare facilities [6]. Additionally, most studies on ESBL-associated HAIs in pediatrics were conducted in specific units or critical care services, such as neonatology or intensive care [9], which may explain discrepancies between the literature and the present study, which included other units affected by bacterial HAIs.

Newborns were the most frequently exposed to ESBL-producing Enterobacteriaceae HAIs, with a predominance of hospitalizations in the neonatology unit. Similar results were found in the study by Hu YJ et al. in 2019, in which they observed a predominance of newborns, accounting for 35.71% of cases [9]. According to their findings, HAI incidence depends on the type of hospitalization unit and the quality of care provided. Our results could be explained by the fact that all HAI cases in the present study were bacteremias diagnosed through blood culture, and the neonatology unit at CHU Mère Enfant Tsaralalàna was the primary prescriber of blood cultures.

After 48 hours of hospitalization, fever was the most frequently observed clinical sign in 79.2% of patients who developed ESBL-producing Enterobacteriaceae HAIs. From a biological perspective, elevated CRP levels were the first biological marker indicating a probable bacterial HAI in this series. Since fever is a defense response of the body to an infection, it is expected to be associated with persistent inflammatory marker elevation (CRP) [10]. Clinical and biological monitoring of patient symptoms at admission and their progression is crucial in managing hospitalized patients, especially children, whose symptoms can vary and evolve rapidly.

Low birth weight was identified as a significant risk factor, exposing patients to three times the risk of developing ESBL-producing Enterobacteriaceae HAIs compared to those with normal weight in this study. This finding is consistent with other studies conducted in Madagascar by Herindrainy et al. in 2018 [11] and globally [10,12-14]. This could be explained by the immaturity of the immune system and the lack of protective flora and mechanical barriers.

Preventing the occurrence of ESBL-producing Enterobacteriaceae HAIs starts with proper pregnancy management and maternal nutrition to ensure full-term births with normal weight. This highlights the crucial importance of well-conducted prenatal consultations to detect any abnormalities in the mother and fetus and to prevent infectious risks, which are common in this population. Raising awareness and educating mothers about prenatal health, perinatal care quality, and the qualification of healthcare personnel providing these services should be reinforced.

Gastric tube feeding and oxygen therapy were other identified risk factors in this study, exposing patients to ESBL-producing Enterobacteriaceae HAIs 6 to 9 times more frequently. A study conducted by Merzougui in a neonatal unit also found gastric tube feeding as a risk factor for ESBL infections, albeit with a twofold increased risk [15]. Regarding oxygen therapy, no existing literature confirms this factor, but the hypothesis of microtrauma caused by the

presence of a nasal cannula or endotracheal tube could be suggested, along with inadequate hygiene and cleaning of these devices, considering that Enterobacteriaceae are commensal bacteria of the digestive flora and can colonize the oropharyngeal area.

Stapleton PJM et al. in 2015 identified understaffing of healthcare personnel as an indirect factor contributing to the emergence of ESBL-producing bacteria [16]. The frequency of gastric tube changes and cleaning after each feeding was questioned. In this study, these processes were not verified due to its retrospective nature. The gastric tube, through inevitable mucosal microtraumas, can be responsible for bacteremia [15], suggesting prior colonization of the oropharyngeal flora by ESBL-producing Enterobacteriaceae.

According to Andrianarivelo et al. in 2009 and Herindrainy et al. in 2018, a significant probability of antenatal acquisition of ESBL-producing Enterobacteriaceae was observed in their studies [17,11], which could support the findings of this study on gastric tube feeding and oxygen therapy, both involving the rhinopharyngeal region and potentially affecting patients already colonized by multidrug-resistant Enterobacteriaceae. Further studies on oropharyngeal ESBL carriage in pediatric patients could be suggested to support this hypothesis [6].

In a report by Baltimore RS in 2012, patients who received antibiotics in their study had a higher prevalence of gram-negative bacilli in the pharynx. This phenomenon was attributed to the suppression of normal flora by antibiotics, allowing new organisms to colonize mucosal surfaces. Although antibiotic use upon admission did not show a significant association with the occurrence of ESBL-producing Enterobacteriaceae HAIs in our study, it was observed that 92.4% (n=49) of patients received antibiotic therapy at admission, including 93.8% treated with third-generation cephalosporins, which could support these hypotheses.

Given these factors, breastfeeding is encouraged as soon as the baby's condition permits, as it could reduce the need for gastric tube feeding [18]. Invasive procedures should be minimized in frequency and duration. Care protocols for nasogastric tubes and oxygen therapy devices, including their cleaning and monitoring, should be updated and made available to all personnel, who should be trained accordingly.

From a microbiological perspective, Enterobacter spp. and Klebsiella spp. were the predominant ESBL-producing Enterobacteriaceae species in this study, consistent with the findings of Kilic et al. [6]. The study conducted by Herindrainy P et al. also reported the emergence of neonatal infections caused by ESBL-producing Enterobacter spp. in low-income countries [11]. Meanwhile, a descriptive study by Andrianarivelo AM et al. in 2009 in the intensive care unit of CHU GOB Maternité Befelatanana, Antananarivo, Madagascar, reported the isolation of ESBL-producing Klebsiella spp. as a causative agent of neonatal infections [17]. From a therapeutic standpoint, early detection of ESBL-producing Enterobacteriaceae infections is crucial, as treatment options are limited, especially for neonates and children [17]. In this study, 86.8% and 79.2% of ESBL-producing strains were resistant to gentamicin and ciprofloxacin, respectively. Amikacin and imipenem remained the most effective antibiotics and were frequently used to treat these HAIs, a finding previously reported by Andrianarivelo A et al. in 2010.

The use of broad-spectrum antibiotics, often the last resort for treating multidrug-resistant HAIs, can be life-saving but also increases the risk of emerging highly resistant strains (HRB), leading to therapeutic impasses and potentially fatal outcomes.

CONCLUSION

At the end of this study, it appears that the overall rate of healthcare-associated infections (HAIs), as well as those associated with extended-spectrum beta-lactamase-producing Enterobacteriaceae (ESBL-PE) at CHUMET, is lower compared to other studies conducted abroad. The affected population was predominantly newborns, a high-risk and highly vulnerable group due to the immaturity of their immune system.

The microbiological documentation of ESBL-PE-associated HAIs highlights the crucial need for all pediatric patients to have access to high-quality diagnostics to optimize the appropriate management of all hospitalized Malagasy children in public healthcare facilities. The microbiological findings are consistent with other national and international studies regarding the predominance of Enterobacter sp. and Klebsiella sp. species, which are frequently involved in HAIs due to their ability to survive in hospital environments.

This study underscores the importance of monitoring HAIs and the emergence of multidrug-resistant and highly resistant bacteria in all pediatric healthcare facilities. It also emphasizes the critical role of the infection prevention and control (IPC) team in these surveillance activities, as well as in the implementation, application, and monitoring of infection control measures in pediatric institutions.

Multicenter studies on the antenatal colonization of ESBL-PE strains in the digestive tract and pharynx of patients admitted to pediatric healthcare facilities would be necessary to support the findings of this study. Additionally, further research on the economic impact of HAIs in general, and those caused by ESBL-PE in particular, would help guide strategies and allocate necessary funds for IPC activities, which are fundamental to the quality of care in healthcare institutions.

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