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EPIDEMIOLOGY OF NEWBORN COLONIZATION BY ESKAPE PATHOGENS ON A 20 YEARS PERIOD

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Abstract: Infections caused by antimicrobial resistant microorganisms have become more prevalent in the last decades, and are part of a serious public health issue worldwide. In the neonatal intensive unit therapy (NICU), prolonged hospitalization, major use of antimicrobials and invasive procedures, along with immature immunological system, are all risk factor for multidrug-resistant microorganisms' acquisition. The objective of this present study was to evaluate the epidemiological tendency of colonization by ESKAPE pathogens in newborns in the NICU on a 20 years period. Vigilance swabs cultures were analyzed from january 2000 to december 2019. Only the first positive culture of each NB was considered for microorganisms frequency. Amongst the most frequent microorganisms identified were Gram-negative bacilli (929/1107 – 84%). Extended spectrum Beta lactamase producing Enterobacterales (ESBL) were responsible for 753 (70%) colonization. Carbapenem resistant Enterobacterales was seen in smaller frequency (2%). The mean of incidence density of ESBL *Klebsiella pneumoniae* during the period were 2.3/1.000 patients-days, and it variated from zero in 2000 to 5 in 2013, 2015, 2018 and 2019. Amongst Gram positive cocci, the most frequent were methicillin resistant *Staphylococcus aureus* (MRSA), with 11%, and vancomycin-resistant *Enterococcus faecium* (VRE), in 5% of the vigilance cultures. The pathogens incidence of ESKAPE group were elevated in 20 years, and *K. pneumonie* was the most frequent colonizing pathogen in NB. Considering that colonization usually precedes infection, and there is high mortality associated with multidrug-resistant microorganisms, the elevated frequency of the ESKAPE group is quite worrying and requires control and preventive measures.

Keywords: Enterobacterales; Newborns; Multidrug-resistance; Beta-lactamases;

Gram-positive cocci; Gram-negative bacteria

INTRODUCTION

Newborns in the Intensive Therapy Unit (NICU) are at high-risk developing infections due to the invasive medical devices and the prolonged hospitalization. Irresponsible use of antimicrobials favors multidrug-resistant microorganisms selection and consequently, colonization by these pathogens (CLOCK et al., 2017b; NORDBERG et al., 2018a)4% and 1% of the infants were colonized with MRSA or VRE, respectively. Predictors identified in fixed-effects models were surgery during hospitalization (for MRSA colonization.

In this scenario, pathogens designated by the acronym "ESKAPE" (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, Acinetobacter baumannii* and other Enterobacterales) are associated with elevated morbidity and mortality rates (OLIVEIRA et al., 2020).

Many studies have indicated the multidrug-resistant pathogens colonization frequency in adults, but few data have showed the frequency in a prolonged time with the pediatric population (WEINER et al., 2016). Considering the multidrug-resistant microorganisms colonization frequency rates can provide important information to implement adequate antimicrobial therapy and control measures, the present study aimed to evaluate colonization epidemiology by ESKAPE pathogens in NICU hospitalized newborn, in a 20-year period.

MATERIALS AND METHODS

This retrospective, transversal and descriptive study was made in the neonatal unit of HU-UEL, a tertiary University Hospital in South Brazil. The data collected was between January 2000 and December 2019. HU-UEL's maternity facility is reference for high-risk pregnancy medical care, and it is where most newborn come from to be hospitalized in the neonatal unit. The neonatal unit includes the neonatal intensive care unit (NICU), and the neonatal intermediate care unit (INCU), which is composed by 30 beds, and has hospitalized 11.736 newborns in this 20 years period.

Vigilance colonization swabs were previously made, and the results were taken from the Information System AGTA Healthcare LABHOS from the clinical analysis laboratory from HU-UEL (LAC/HU) data bank. The presence of vancomycin-resistant *E. faecium* (VRE), Methicillin-resistant *S. aureus* (MRSA), carbapenem-resistant *A. baumannii* and P. aeruginosa (NF-GNB CR), third and fourth generation cephalosporin resistant Enterobacterales (ESBL) and carbapenem resistant Enterobacterales (CRE) were evaluated.

ESKAPE group microorganisms were identified using Jorgensen et al. (2015) methods, and antimicrobial sensitivity was determined by CLSI methods. ESBL production was evaluated using the disc proximity method, and carbapenem resistance was determined by disc diffusion method. Cefoxitin and Vancomycin disc diffusion were made to identify MRSA and VRE.

Colonization Incidence density was obtained dividing new case numbers by patient-days that were hospitalized in the unit in the same time period, and multiplying by 1.000, according to the hospital's statistics unit (SAME/DAME).

This study was approved by the ethical committee involving humans from Londrina's State University, under the number CAAE 43013315.8.0000.5231.

RESULTS

From January 2000 to December 2019 there were 11.736 admissions in the neonatal unit, with 133.586 patient-days, and a total

of 10.967 newborns. Annually, 2.000 patients were admitted in the neonatal unit. ESKAPE pathogens were identified in 2.690 samples. Double samples excluded, there was 1.078 newborns were colonized by these pathogens (figure 1).

In 20 years, Gram-negative microorganisms were the most prevalent (926-86%). Amongst these, 749 (70%) were 3rd and 4th generation cephalosporines resistant Enterobacterales, 26 (2.4%) were CRE and 148 (14%) CR NF GNB. The more frequent ESBL producing bacteria were *K. pneumoniae* (356) 33%, *S. marcescens* (177) 16%. *E. cloacae* (149) 14% and *E. coli* (49) 4,5%. The investigated CR NFB *A. baumannii* and *P. aeruginosa* were identified in (105) 10% and (43) 4% cultures, respectively. Between Gram-positive, (102) 10% were MRSA and only (43) 4% were VRE (Figure 2).

Until 2000, ESKAPE pathogens prevalence in the neonatal unit was rare, and the first colonization by GNB was reported in 2001. It was observed that until 2019 the incidence of multidrug-resistant GNB grew, with some fluctuations in the period. The mean of the incidence density from 2000 to 2019 was 7.6 GNB by 1.000 patient-days. The number grew to 16 in 2008, dropped to 5.8 in 2012, and grew again to 14 in 2014 and 15.2 in 2018.

For Gram-positive cocci, the mean of the incidence density was 1.5/1000 patient-days. The highest rates were seen in 2006 (6.8) and 2007 (5.9), but decreased over the years, with oscillations in 2012, 2018 e 2019. Once Gram-negative bacilli appear in the hospital units, they tend to compete with Gram-positive cocci. Therefore, GNB had a peak in 2003 and maintained high over the years, with a slight decrease in 2004, 2009 and 2010, a high incidence density in 2008 (16.0 ID) and 2018 (15.2 ID), exceeding the limits of control, evidencing an outbreak. These results for GNB happened at the expense of Enterobacteraes (figure 3).

CRE incidence density was 1.2/1.000 patients-day, but for ESBL it was 15/1.000 patient-days in 2008, showing a fall over the following years, and rising up again in 2014 and 2018, with fluctuations over the years.

The highest incidence density for CRE happened in 2007, with *A. baumannii* and *P. aeruginosa*, but it lowered in the following years (figure 4).

Regarding the species of the microorganism, between 2005 and 2011, only NF-GNB were carbapenem resistant, in 2014 and 2018 there was an *A. baumannii* outbreak. The first CRE reports happened in 2012, with incidence density of 0.2/1.000 patient-days, and the most frequent specie was K. pneumoniae. In 2014 happened the first CRE outbreak, when incidence density was 1.5/1.000 patient-days. Between 2015 and 2016 there was no case identified, but it rose again in 2017 (figure 5).

As for Gram-positive cocci from ESKAPE group, there was a VRE outbreak from 2006 to 2008, and the density went from 5 to 1.2. Except for this period, the mean of the incidence density was 0.121.000 patient-days. After 2012, the frequency of VRE progressively decreased to almost zero until 2019. MRSA incidence variated from 0.4 in 2000 to 3.51.000 patient-days in 2007, suggesting an outbreak during this period. It was observed a decrease in MRSA, keeping the mean at 0.66/1.000 patient-days until 2018, when it rose again to 2.9 (figure 6).

DISCUSSION

The present study showed a high colonization frequency by ESKAPE microorganisms in newborns for the last 20 years. ESBL producing bacteria, especially K. pneumoniae, disseminated, and the incidence density grew.

The frequency and diversity of the species can differ according to the place and the presence of an outbreak. In the last decade,

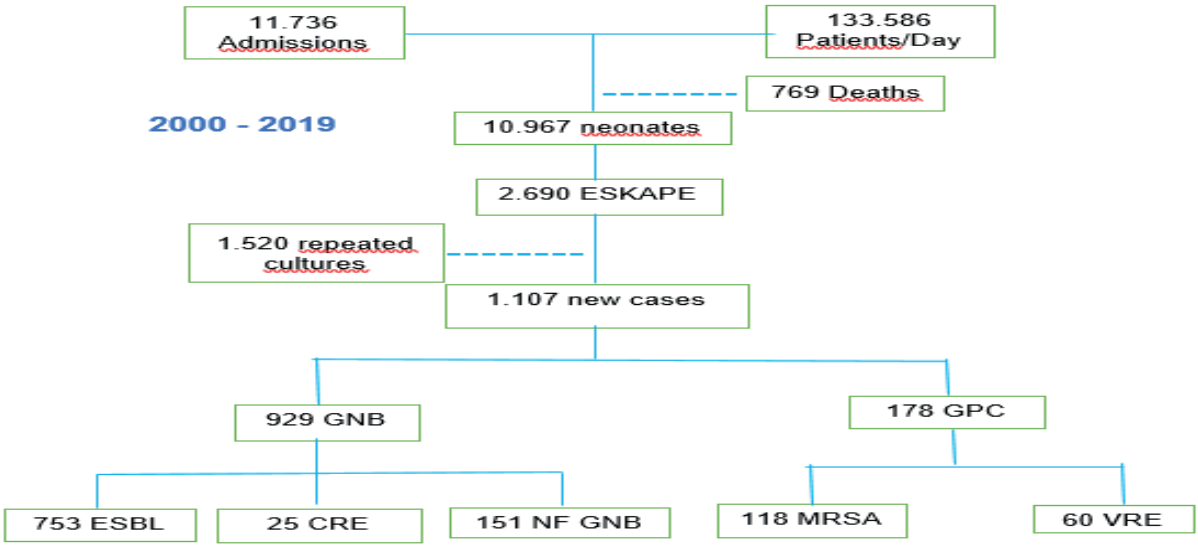

Figure 1: Total admission number and patient-days and amount of microorganisms colonizing newborns hospitalized between 2000 and 2019.

Abbreviations: ESKAPE: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa e Enterobacter spp*. GNB: Gram negative bacilli. GPC: Gram-positives cocci. ESBL: extended spectrum beta lactamase. CRE: carbapenem resistant Enterobacteracae. NF GNB: Non fermenting Gram negative bacilli. MRSA: Methicillin resistant Staphylococcus aureus. VRE: vancomycin resistant entecococcus faecium.

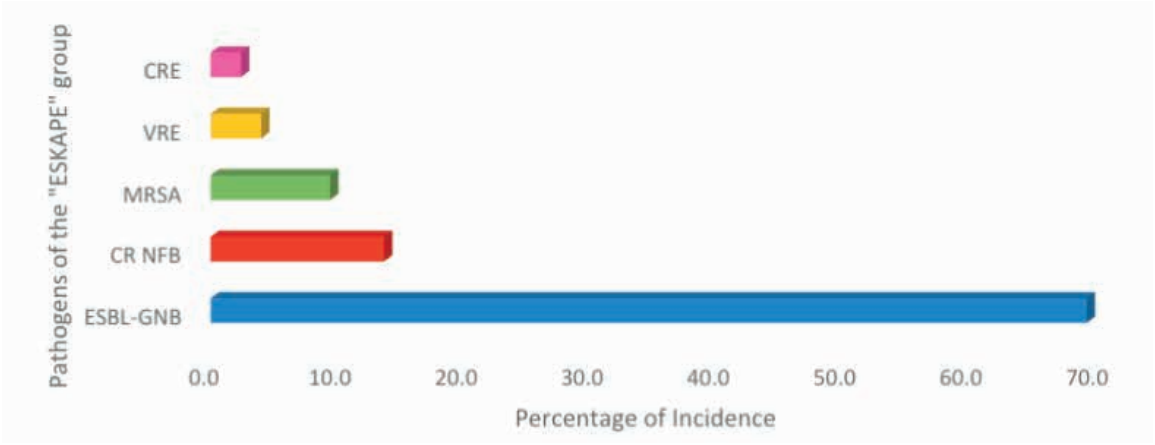

Figure 2 – Percentage of frequency of colonization by ESKAPE pathogens of 1.078 newborns in the NICU, between January 2000 to December 2019.

Abbreviations: ESBL-GNB: extended spectrum beta lactamase producing Gram-negative bacilli. CR NFB: carbapenem resistant non fermenting Gram-negative bacilli; MRSA: Methicillin resistant *Staphylococcus aureus*; VRE: vancomycin-resistant *Enterococcus faecium*; CRE: carbapenem resistant Enterobacterales.

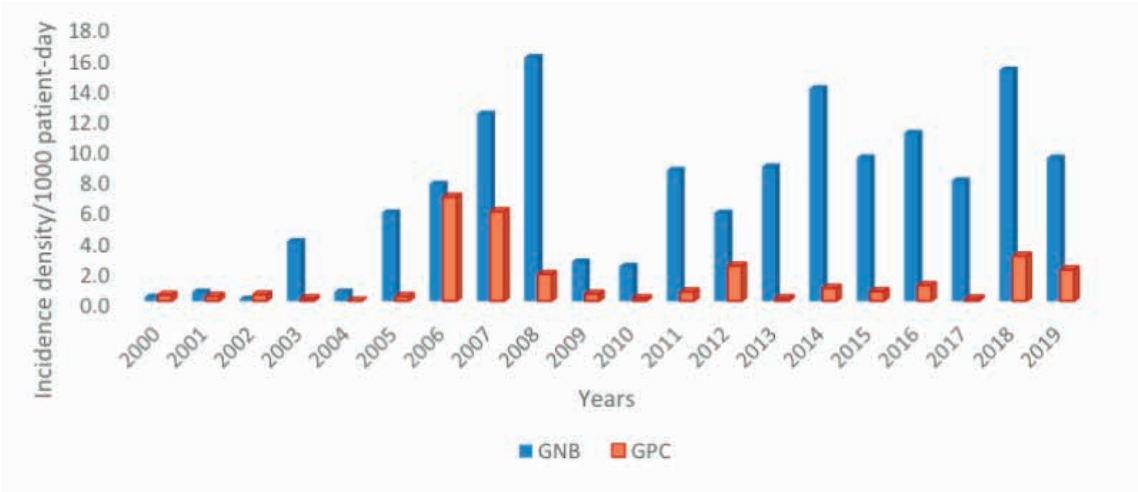

Figure 3 – Incidence density of colonization by Gram-negative bacilli and Gram-positive cocci from ESKAPE group, isolates from newborns in the NICU of a hospital in south brazil, between January 2000 to December 2019.

Abbreviations: GNB Gram-negative bacilli; GPC – Gram-positives cocci.

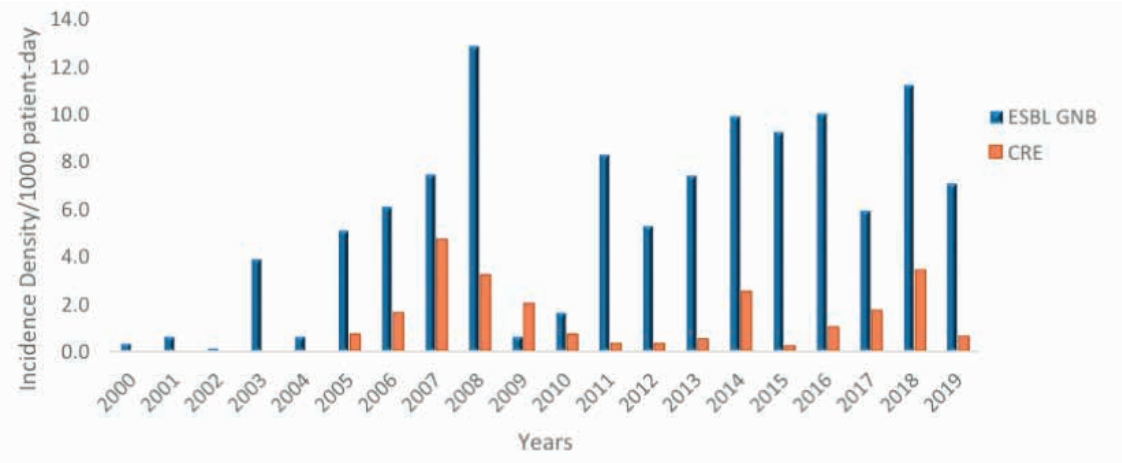

Figure 4 – Colonization incidence density by ESBL producing Gram-negative bacilli, and carbapenem resistant, isolated from newborns in the NICU of a hospital in south Brazil, between January 2000 to December 2019.

Abbreviations: ESBL GNB – Extended Spectrum beta-lactamase Gram-negative bacilli. CRE – Carbapenem resistant Enterobacterales.

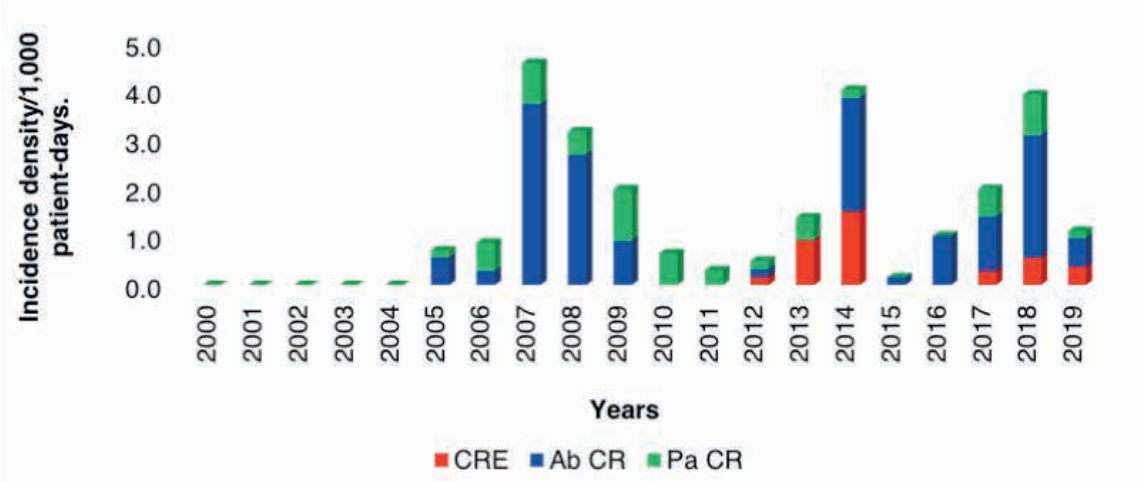

Figure 5 – Incidence density of carbapenem resistant Gram negative isolated from newborns in the NICU of a hospital in south Brazil, between January 2000 to December 2019.

Abbreviations: CRE – Carbapenem resistant Enterobacterales; Ab CR – carbapenem-resistant *Acinetobacter baumannii*; Pa CR – Carbapenem-resistant *Pseudomonas aeruginosa*.

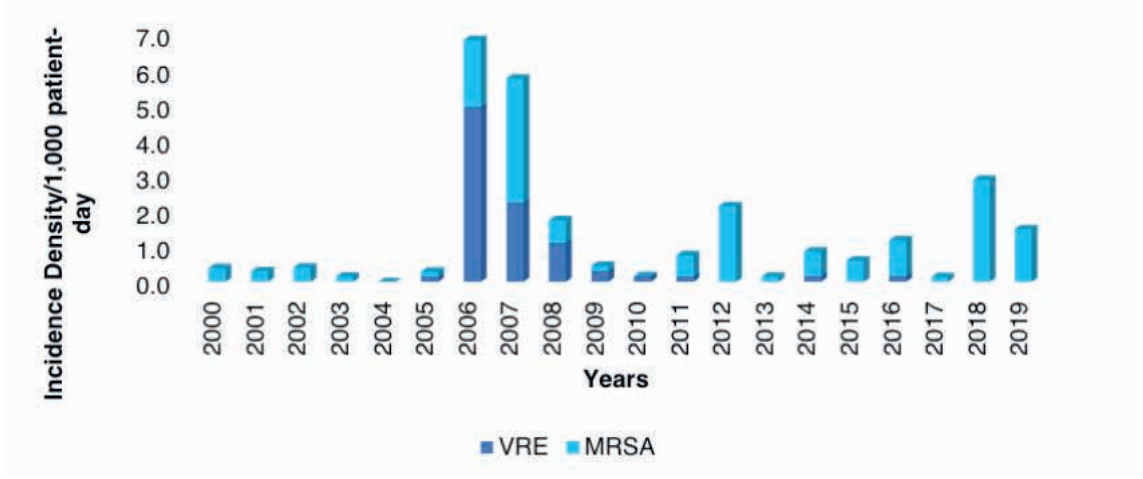

Figure 6 – Incidence density of ESKAPE group Gram-positive cocci colonization, isolated from newborns in the NICU in a hospital in south Brazil, between January 2000 to December 2019.

Abbreviations: VRE – Vancomycin resistant *Enterococcus faecium*; MRSA – Methicillin-resistant *Staphylococcus aureus*.

studies showed a high prevalence of multidrug-resistant Gram-negative bacteria colonizing hospitalized newborns in the neonate unit (BAIER et al., 2019; LEIKIN-ZACH et al., 2018; OLIVEIRA et al., 2020; ROBERTS et al., 2019) with colonization and blood stream infections being a major threat to this population. Since 2013, all NICU admissions at our facility were screened twice weekly for ESBL colonization. OBJECTIVES To determine independent risk factors for colonization of infants with ESBL-producing bacteria in the NICU. METHODS A retrospective case study of ESBL-colonized infants vs. controls (matched by date of birth and gestational age.

In 2015 to 2017, data from the National Healthcare Safety Network (NHSN) showed ESKAPE pathogens to be the most common in healthcare associated infections in the United States. *S. aureus* was responsible for 15.4% of these infections, followed by *E. coli* (12,3%), *K. pneumoniae* (9,3%), *Enterococcus* spp. (8,7%), *Enterobacter* spp. (8,5%) and *P. aeruginosa* (5,8%) (WEINER-LASTINGER et al., 2020). On the contrary, in our study the frequency was higher for Gram-negative bacteria, such as *K. pneumoniae, E. cloacae e S. marcescens*.

In a systematic review published by Folgori et al. (2018), 28.7% of newborns (1.825/6.363) were colonized, and 7.9% (157) developed bloodstream infection by GNB. Accordingly, in our study, most colonizers were GNB fourth generation cephalosporin resistant.

Latin American and other developing countries usually have higher rates of bacterial resistance in comparison to European countries and the United States, especially between NF-GNB and ESBL producing *Enterobacteriales* (GHADDAR et al., 2020; MARRA et al., 2011; NORDBERG et al., 2018a; SILVA, 2016)Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp., capable of scaping the action of the antibiocts by representing resistance. The goal of this study is to trace the ESKAPE pathogens antimicrobial susceptibility profile in a primary public hospital in the Federal District, Brazil. A cross-sectional, retrospective and descriptive study was conducted by analyzing the corresponding data from january 2010 to december 2015 for samples that were positive for microorganisms of ESKAPE pathogens. Analyzing the gram-positive almost 80% of E. faecium were vancomycin-resistant enterococci (VRE.

ESBL producing E. coli and KPN in Latin American Countries is a well known situation, and it's responsible for high rates resistance to broad spectrum cephalosporin (GHADDAR et al., 2020; MARRA et al., 2011; NORDBERG et al., 2018a; SILVA, 2016)Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp., capable of scaping the action of the antibiocts by representing resistance. The goal of this study is to trace the ESKAPE pathogens antimicrobial susceptibility profile in a primary public hospital in the Federal District, Brazil. A cross-sectional, retrospective and descriptive study was conducted by analyzing the corresponding data from january 2010 to december 2015 for samples that were positive for microorganisms of ESKAPE pathogens. Analyzing the gram-positive almost 80% of E. faecium were vancomycin-resistant enterococci (VRE.

Saleem et al. (2020) showed that ESBL producing GNB colonized healthy community newborns, with a frequency of *E. coli* (84%), *K. pneumoniae* (10%) and *Enterobacter* spp. (6%), whereas in our study, colonization was mainly by *K. pneumoniae* and *S. marcescens*. A possible explanation is because our isolates are hospital associated.

Studies from Europe reported fewer multidrug-resistant GNB. Colonization in

Italy was 28% (Giuffrè et. Al 2016a). In a retrospective study conducted by Haase et al (2014), 4.9% of newborns developed infection by MR ESKAPE pathogens. The colonization incidence density by MR Enterobacterales in this study was 3.5/1.000 patient-day in 2012, which is lower than the one found in our study, although it has also presented growth over the years. Baier 2019 also reporte GNB to be the most frequent (26%).

Carbapenem-resistance is disseminating globally, and the numbers varies according to the place and time of the study (FOLGORI et al., 2018; SALEEM et al., 2020)we aimed to estimate the prevalence of gut colonization with extended spectrum beta-lactamase (ESBL. In a study published in Thailand, 57% of *A. baumannii* and 52% of *K. pneumoniae* were resistant in newborns, numbers higher than ours were. KPC producing *K. pneumoniae* in newborns was first reported in Pakistan in 2008, and in 2011, 72% of isolates were KPC (SALEEM et al., 2020)we aimed to estimate the prevalence of gut colonization with extended spectrum beta-lactamase (ESBL. In this study, the first CR GNB was reported in 2005, in *A. baumannii* and *P. aeruginosa*. It was only in 2012 that CR Enterobacteriales was identified, in *K. pneumoniae*, *E. cloacae* and *S. marcecens*, but our rates were lower than other countries.

Among ESKAPE Gram-positive cocci, *S aureus* is one of the main infection pathogens and it's known worldwide to affect newborns. Many studies reveal that MRSA colonization in newborns is a risk factor for infection development (LYLES et al., 2016).

Data published from ECDC in 2019 disclose that MRSA prevalence in Europe fluctuates from 0% (in Island) to 43% (in Romania) (ECDC, 2019). Studies made in neonatal units in Germany found low frequencies of MRSA in newborns (BAIER et al., 2019; HAASE et al., 2014)these infants acquire commensal bacteria, which might become potentially harmful. On-ward transmission of these bacteria can cause outbreaks. Aim: To report the findings of a prospective surveillance of bacterial colonization and primary sepsis in preterm infants and neonates. Methods: The results of the surveillance of bacterial colonization of the gut and the respiratory tract, targeting meticillin-resistant Staphylococcus aureus (MRSA. Our data fluctuated in our analysis period. In 2007 happened the highest incidence density of MRSA/1.000 patient-days. Our rates were lower than that most of the time.

Just like MRSA, VRE frequency has fluctuated in neonatal units, and is associated with outbreaks. VRE frequency has a growing tendency, according to ANDERSSON et al. (2019).samples (surface swabs and rectal swabs From 1.5% to 17.3% in 2018, it has been a matter of concern in European hospitals, reinforcing the need to better understand the local epidemiology, clonal diversity and infection associated risk factors (ECDC, 2019).

In opposition to some German studies, on which VRE were not detected, our hospital suffered an outbreak in the NICU in 2005. Data from previous studies in our hospital showed a VRE outbreak related to the contaminated environment between 2004 and 2007 in adult ICU.

Vigilance cultures in neonatal units are a simple, yet, effective intervention to prevent infection outbreaks (HEINRICH et al., 2011; HUANG, et al., 2002). Prevention, according to Moreira, et. al. (2011), is the main resource to stop colonization in the NICU, since treating infections is challenging due to antimicrobial resistance.

After all these considerations, surveillance must be made in neonatal units, along with microorganism identification, prevention, and infection control (CÔRTES; BASTOS, 2014).

CONCLUSION

There was a high epidemiological tendency in colonization by ESKAPE microorganisms, especially Gram-negative bacilli. ESBL producing bacteria, especially *K. pneumoniae* were the microorganisms that most frequently colonized hospitalized newborns. A slight fluctuation in the rates was seen, probably related to outbreaks along the years.

Strict prevention techniques and infection control should be adopted, such as hand hygiene, personal protective equipment use, fewer use of invasive medical devices and antimicrobial control. In addition, vigilance swab cultures, proper cleaning and staff training can reduce colonization by ESKAPE microorganisms.

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