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Original Research Article

Neonatal Septicemia: Clinical and Epidemiological Features

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Abstract

Introduction: to compare the clinical, biological, and evolutionary profiles of sepsis with multi-drug resistant and non-multi-drug resistant bacteria in the newborn population. ***Methods:*** we performed a prospective, observational, comparative study to monitor all the episodes of blood stream infection, received from the neonatal intensive care, from June to December 2019. Collected data included demographics, symptoms at the time of sepsis, laboratory values, microbiologic results, preliminary and final outcomes. ***Results:*** Out of 219 positive blood cultures, 93 episodes were retained. The median age was 6,66 days, 63.4% of newborns were male and 62,4% were premature, 39% of whom had a gestational age of less than 34 weeks. Multidrug-resistant (MDR) bacteria caused 68 sepsis episodes, while non-MDR resistant bacteria caused 25. Bacteremia with MDR organisms, in comparison with non-MDR organisms was associated with poorer preliminary outcomes after empirical antibiotherapy (14% vs 32%; P= 0,001), higher overall mortality rate (20% vs. 51%, P =0.003), and longer antibiotic intake (9.84 vs 7.56 ; P=0,02). The major risk factor found is prematurity (70% vs 40%, P<0,001), No statistical significance was found when other clinical features or laboratory values were compared for infections with MDR vs. non-MDR bacteria. ***Conclusion:*** Septicemia with MDR bacteria is more common than non-MDR one in NICU, and it is related to higher morbidity and mortality rates.

Keywords: neonatal-septicemia-multi-drug-resistance.

INTRODUCTION

Neonatal sepsis is the third leading cause of neonatal mortality and a major public health problem[1], especially in preterm newborn. Early diagnosis and appropriate therapy of septicemia is important to prevent morbidity and mortality.

Blood culture is still the gold standard among diagnostic methods for detecting microbial etiology of newborn infection[2]. The availability of enriched media that have passed quality control standards, as well as the ability to sustain the growth of fastidious organisms and negate the action of antibiotics contained in the specimens, has improved blood culture methods in recent years[3].

All of these advancements, however, could be endangered if blood cultures are contaminated, resulting in false-positive results[4]. Because the clinical relevance of probable contaminants is unknown, it leads to lengthier hospital stays, needless antibiotic therapy, and more laboratory testing; as a result, and consequently, a higher cost of hospitalization. [5].

Within the last decade, multi-drug resistant organisms (MDROs) have been emerging as important pathogens that cause sepsis in the neonatal intensive care units (NICU), including gram-negative producing extended-spectrum beta- lactamase (ESBL), cephalosporinases, and carbapenemases [6], methicillin-resistant *Staphylococcus aureus* (MRSA), MDR *Acinetobacter baumannii* (MRAB)[7].

The aim of this study is to evaluate the correlation between bloodstream infection in the neonatal intensive care unit (NIUC) and their clinical relevance.

MATERIALS AND METHODS

From June to December 2019, we conducted a prospective, observational, longitudinal study in the NICU in Mohammed VI University Hospital Center in

Marrakech, to monitor bloodstream infection in hospitalized newborns.

The blood culture was performed as 1-2 mL of venous blood was inoculated into the blood culture bottle. The samples were processed by standard bacteriological procedures. The identification was performed by the BD Phoenix automated microbiology system (Becton Dickinson), as was the antimicrobial susceptibility testing, which was confirmed by the Kirby-Bauer disc diffusion susceptibility method in accordance with the European Society of Clinical Microbiology and Infectious Disease guidelines[8].

For this analysis, cultures isolates growing coagulase-negative *Staphylococcus*, *Corynebacterium* spp and *Bacillus* spp are considered as contaminants [9]. Also, bacteremia without clinical or biological relevance is considered as a contamination.

Collected data included demographics, gestational age, weight at birth, signs of sepsis at time of blood culture draw, comorbidities, presence of central venous catheter, laboratory values at time of sepsis, previous antibiotics exposure, Results with empirical antibiotherapy and after adjudication according to the antibiogram.

Summary statistics of the demographic and clinical characteristics of all patients were expressed as frequencies and proportions for categorical variables, mean ± SD or median and interquartile for continuous variables.

The association between categories is measured by the Chi square test, and by the student T test for continuous variables. $P < 0.05$ was recognized as statistically significant. All these statistical calculations were performed using the SPSS 25.0 software (SPSS Inc, Chicago, USA).

RESULTS

93 episode of blood stream infection was retained from a total of 224 positive blood cultures. 126 of which were excluded for the lack of clinical information or whether they were second or third samples, or cultures were considered contaminated with a contamination rate of 31%.

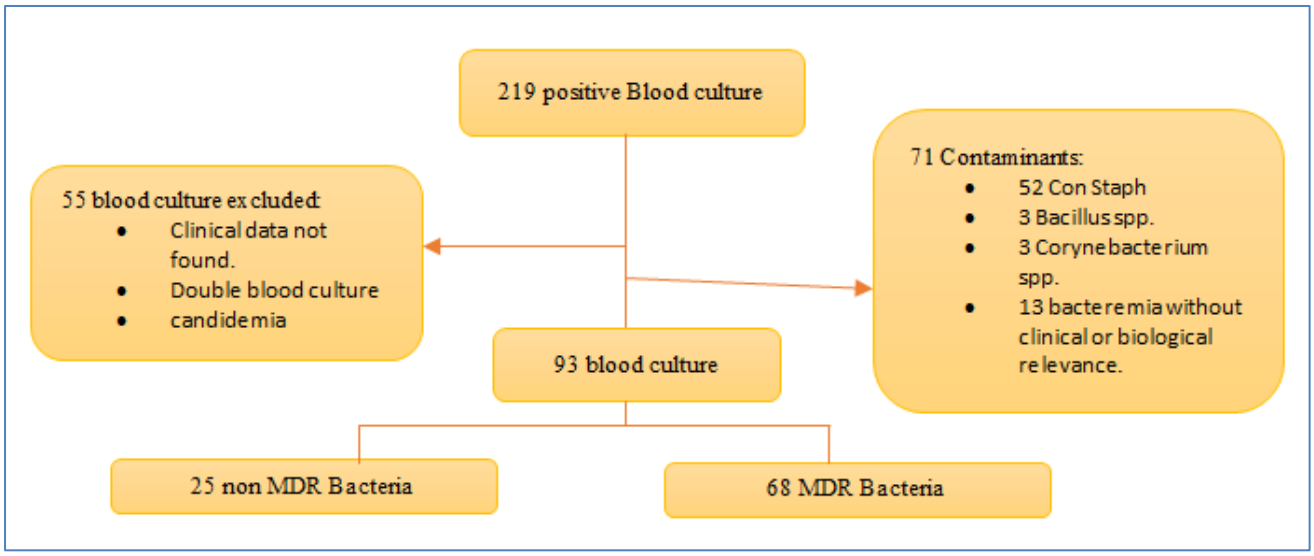

Fig-1: The distribution of positive blood culture in the study:

The average age of our newborn population was 6, 66±7,97days, 63.4% of newborns were male with a sex Ratio M/F sex ratio of 2, 7. The average weight was 2.16± 0, 94 kg. 62,4% (n=58) of patients were premature, 39% of whom had a gestational age of less than 34 weeks.

Respiratory distress is the most common symptom in our infant population, followed by jaundice and convulsions.

In terms of clinical diagnosis of sepsis, it was only found in 11% of the patients with symptoms of circulatory failure.

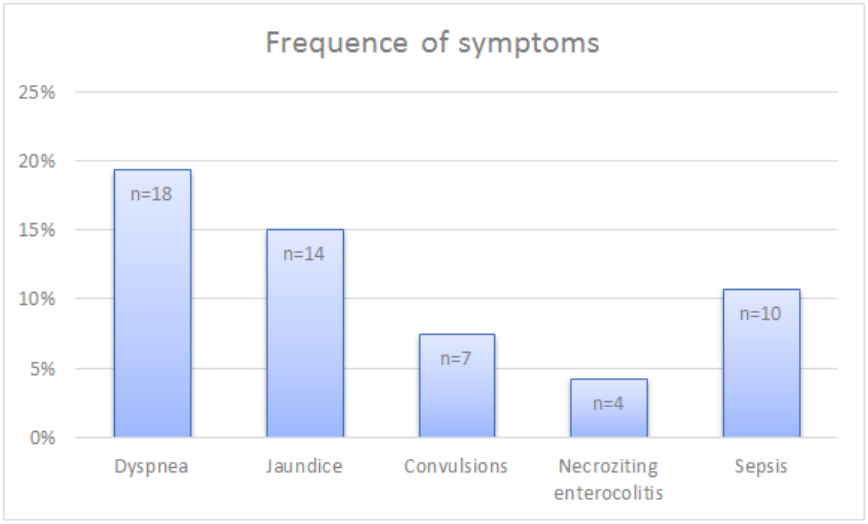

Fig-2: Organigram presenting the most relevant symptoms

Non-BMR bacteremia was caused by various bacterial species: Enterobacteriaceae (24%), *Streptococcus spp* (37%), *Pseudomonas aerogenosa* (20%) and Methicillin-sensitive *Staphylococcus aureus* (16%)

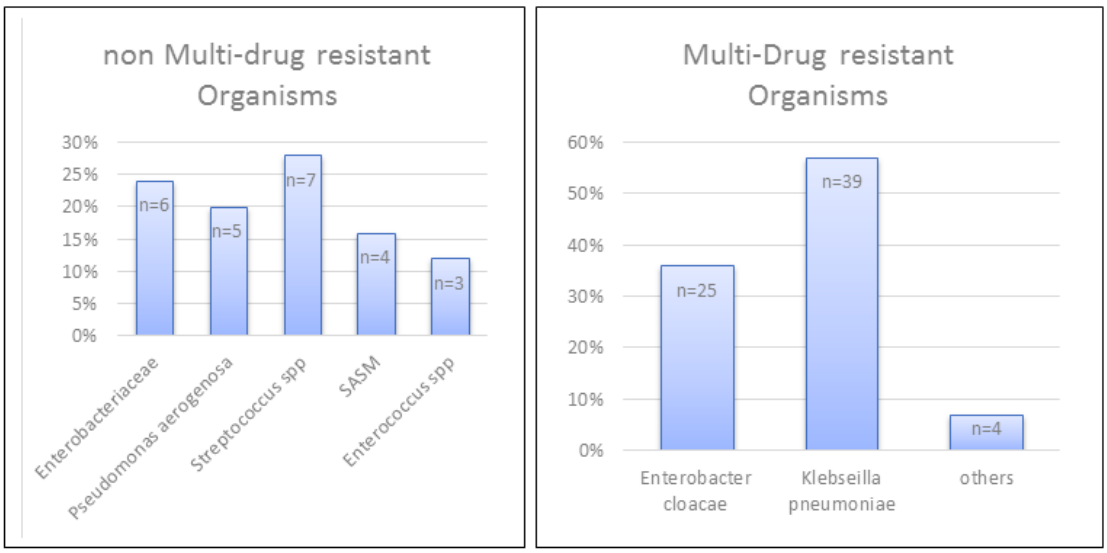

Fig-3: The prevalence of different bacterial species

Among the patients with *Streptococcus spp* septicemia, group B *Streptococcus* (GBS) was present in only 28% (n=2) of cases with an overall prevalence of 2%, 28% (n=2) of sepsis were caused by group A streptococci, and 28% (n=2) by group D non-enterococcal streptococcus and one case of late onset septicemia with *Streptococcus pneumoniae*.

Klebsiella pneumonia was the most common pathogens in this study, with a prevalence of 41% (n=39), followed by *Enterobacter cloacae* at 26% (n=25). The most prevalent resistance mechanism was ESBL secretion, which is detected in 97% of the strains, followed by carbapenem resistance encountered in 41% of resistant Enterobacteriaceae, which was first observed for Ertapenem and then for Imipenem and Meropenem.

When the initial empiric antibiotherapy failed to provide adequate antibacterial coverage based on clinical outcomes and the antimicrobial susceptibility test, the regimen had to be switched to antibiotics with broad spectrum antibiotics.

The clinical, biological and evolutionary data of newborns with sepsis with MDR bacteria in comparison with those non-MDR bacteria are noted in the underlying table.

Table-1: Clinical, demographic, preliminary and final outcomes in newborn population with MDR bacteremia in comparison with non MDR ones:

	Blood stream infection with MDR Bacteria	Blood stream infection with NON-MDR Bacteria	P
Age	3.29	7.57	0.10
Prematurity	70% (n=48)	40% (n=10)	<0.001
Weight	2.11 ± 0.94	2.37 ± 0.97	0.064
Positive infection history	26%(N=18)	72% (N=18)	<0.001
C-reactive protein	75.89 ± 57.07	62.18 ± 76.42	0.23
Platelets	154.24 ± 143.72	235.64±101.01	0.11
Leukocytes	14.34 ±10.19	11.33 ± 6.32	0.21
ATB durations	9.84 ± 6.38	7.56 ± 3.7	0.02
Remission after empirical antibiotherapy	14% (n=10)	32% (n=8)	<0.001
Mortality with empirical ATB	25% (n=17)	4% (n=1)	<0.001
Overall remission	48% (n=33)	80% (N=20)	0.001
Overall mortality	51% (n=35)	20% (n=5)	0.003

When compared with non-MDR Bacteria, sepsis due to MDR organisms (MDRO) was associated with a higher overall mortality rate (20% vs. 51%, P =0.003), and poorer targeted overall remission (48% vs. 80%, P = 0.001). Univariate analysis also found that sepsis due to MDR Organisms was associated with Prematurity (P< 0,001), and longer antibiotic intake (9,84 vs 7,56, P=0,02). The age, C-reactive protein (CRP) values, leukocytes count seems to be higher and Platelets to be lower in the MDRO infection in comparison with non-MDR, but without statical significance.

Infection with Non-MDR bacteria was associated with positive infection history (72% vs 26%; P<0,001). The 5 cases presented with *Pseudomonas aerogenosa* bacteremia had poor outcomes, even if the strains only expressed their natural resistance, the initial antibiotic therapy was not appropriate in 3/5 of the cases, and the overall mortality was very high at 80% (n = 4).

DISCUSSION

In the NICU, neonatal septicemia is the main cause of infant mortality and morbidity. The incidence in the NICU range from 6% to 57%[10], The variances are indeed wide, depending on parturient compliance with the pregnancy monitoring program, delivery conditions, and antimicrobial measures used in neonatal intensive care units and effective control in spread of nosocomial infection [10,11].

Blood cultures are the gold standard test for the diagnosis of bacteremia, However, the growth of contaminants in blood cultures presents a diagnostic challenge for clinicians and weakens the reliability of blood culture results [12].

Blood culture contamination rate in adult are between 0,6 and 6%, but it range from 0,5 to 22,8% in neonatal population [4,12]. This high rate of contamination is due mainly to difficulties in blood sampling [13].

We found a contamination rate of 31%. Admittedly, there were breaches in the aseptic measurements during the sampling, but the most relevant point is the inconsistency of the volume of blood sampled, especially with low-birth-weight premature newborns. it is recommended that a minimum of 1 mL of blood be drawn from neonates with suspected sepsis before starting antimicrobial therapy[14]. When 0.5 mL of blood is inoculated instead of 1 mL, the sensitivity of the blood culture drops by 10%–40% [15].

The methodology to distinguish pathogens from contaminants is very important. It must take into consideration the type of germ, thus Coagulase negative *Staphylococcus* and *Corynebacteirum spp* have been considered as contaminants [9].

Similarly, bacterial growth of the same organism in multiple blood culture bottles or in serial blood cultures and the correlation between drug susceptibility patterns and treatment outcomes are crucial to decide whether to label isolated bacteria as pathogens or contaminants [16].

In our study, newborns with MDR bacteremia were presumably older than those with non-MDR ones. In fact, neonatal septicemia may be divided into 2 subgroups: early onset sepsis, which occurs within the first 72 hours of life, and it is caused by a variety of germs such as group B Streptococcus and multi-sensitive Enterobacteriaceae, probably colonizing the maternal genital tract and acquired by delivery time. The second subgroup is the late onset sepsis, which occurs lately with multidrug resistant organisms acquired from the hospital environment [7,10].

The spectrum of organisms causing neonatal septicemia shows variation in different countries and even varies in hospitals of the same region. Moreover, group of organisms may be replaced by others over a period of time[10].

Considering MDR organisms, carbapenem resistance is a constant concern. It can occur by an enzymatic (carbapenemase production) or non-enzymatic mechanism (ESBL or Cephalosporinase expression and decreased membrane permeability to carbapenems) [6]. Carbapenemase genes are highly mobile, enabling the rapid and frequent transference of multiple other antibiotic resistance genes [17].

Klebsiella pneumoniae, followed by *Enterobacter* spp., are the most common Enterobacteriaceae to acquire carbapenemase genes in neonatal intensive care [6,17,18].

In newborn population, few publications have attempted to identify risk factors and outcome for septicemia with MDR compared with non-MDR organisms. Our data support their findings that septicemia caused by multi-resistant bacteria leads to prolonged delay in receiving appropriate antibiotherapy, a greater overall fatality rate, and an extended antibiotic use. The main risk factor for acquiring such infection is prematurity, colonization with MDR bacteria, renal disease and previous exposure to third generation cephalosporin or Carbapenem [7,19,20].

The incidence of group B *Streptococcus* in EOS has decreased in recent years due to the implementation of screening and treatment programs for colonization of the genital tract by the germ. Most authors did not mention the overall decrease in septicemia rather than the emergence of other germs, notably *E. coli*, *Staphylococcus aureus*, *enterococcus spp*, and group D *Streptococcus* [21-23].

Blood stream infection with *P. aerogenosa* is not usually encountered in NICU, in adult pathology, it is associated with a 20% higher mortality compared to sepsis caused by other pathogens, all the more if empirical antibiotic therapy is inappropriate[24].

CONCLUSION

Sepsis caused by MDR bacteria is a significant health care issue in the NICU. Antibiotic resistance has been linked to a considerable increase in newborn death and morbidity. Consequently, routine antimicrobial susceptibility surveillance and frequent reviews of hospital and national antibiotic policies are required, to provide optimal empiric and targeted antimicrobial therapy.

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