

## **ANALYSIS OF BLOOD CULTURES OF PRETERM NEONATES IN NEONATAL INTENSIVE CARE UNIT AT KING HUSSEIN MEDICAL CENTER**

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### **ABSTRACT**

Preterm birth rates are increasing everywhere., more frequency in premature is responsible about 75% of morbidity and 70% of mortality in the neonatal period in developing countries. Our study aimed to analyze the blood culture results of preterm neonates in neonatal intensive care units (NICU), calculate the positivity rate, time of onset, spectrum of organisms, antimicrobial susceptibility pattern of these microorganisms, the risk factors associated with positive blood cultures and the development of the infection. The study was designed as a retrospective epidemiologic analytical study, neonatal intensive care unit of Al Hussein hospital was included, the blood cultures for preterm were listed during July 2018 and March 2019. Data of positive blood cultures including identification of microorganisms and susceptibility pattern were obtained. (74%) of Neonates had less than 37 weeks ,(13%) of premature had bacteremia, EoNS and LoNS constituted (22%) and (78%) respectively, 46% of preterm deaths in infants less than 37 weeks old were caused by septicemias, Gram negative bacteria was the most common causes of bacteremia ( 56%), Gram positive bacteria was the most common causes of bacteremia in EoNS that causes 47% of infection and the 3 isolated bacterial families (*Acinetobacter baumannii*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa*) were from 88% to 100% resistant to most antibiotics.

**KEYWORD:-** Preterm neonates, neonatal intensive care, Analysis of blood cultures, sepsis.

### **1. INTRODUCTION**

Incidence of preterm birth is rising worldwide because of increased frequency of multiple births due to increasing psychological stress and medically induced preterm delivery, more frequency in premature (G. age  $\leq 36W+6$  days preterm delivery) was responsible about 75% of morbidity and 70% of mortality in the neonatal period in developing countries. (Tracy A. M, et al, 2016)

The term "prematurity" was used to describe live-born neonates that were delivered before the full 36 weeks and six days of gestation. weight of birth was classified using the WHO weight classification system and categorized into extremely low birth weight (ELBW: birth weight less than 1000 grams), very low birth weight (VLBW: birth weight less than 1500 grams) and low birth weight (LBW: birth weight less than 2500 grams). (Wasim Khasawneh 2020)

In Jordan, over 50% of deaths among children under five years old in 2013 occurred during the first 28 days of life, according to local Jordanian statistics, the NMR is

about 15 per 1000 live births using gestational age (GA) of 20 weeks as the age of viability. (Wasim Khasawneh 2020)

In general, systemic bacterial, fungal, and viral infections are referred to as neonatal sepsis, that may be associated with any gradation of symptoms, Neonatologists in NICUs face significant challenges in managing and diagnosing sepsis, Clinical diagnosis is challenging due to insufficient symptoms and signs, Furthermore, laboratory diagnosis takes a long time, therefore empirical antimicrobial therapy must be started until the suspected sepsis is ruled out, On the other hand, more multidrug-resistant organisms limit the available treatment options and postpone the start of a successful course of action. (Wasim Khasawneh 2020)

In developing countries neonatal sepsis - especially preterm with extremely low birth weight (ELBW) infants- associated with significant increase in rate of mortality and morbidity Despite recent improvements in

medical facilities, neonatal sepsis accounts for over one-third (36%) of fatalities. (Chun-Hong Jia 2022)

The most of these deaths occur in developing countries and about one million of these are attributed to infectious including pneumonia, neonatal sepsis, and meningitis. (Wasim Khasawneh 2020)

Several risk factors that make preterm more susceptible to infections, of them: immature immune system of preterm neonates, gestational age, Apgar score, low birth weight, long duration of hospitalization, invasive procedures, endotracheal tubes, umbilical cauterization, total parenteral nutrition, lack of adequate Infection control measures and random use of antibiotics. (Marie Chevallier 2017)

Sepsis of neonatal is caused by Gram-negative and Gram positive bacteria and Candida, The variety of microorganisms causing sepsis varies from area to another even in the same area, This is because the changing pattern of antimicrobial use and different lifestyle, Morbidity and morbidity of neonatal bacteremia differs from hospital to hospital, in developed countries The incidence varies from one to five cases per 1,000 live births, and 49 to 170 per 1,000 live births in developing countries. (Mamta Dhaneria 2018)

Neonatal sepsis is categorized into two categories: Early-onset neonatal sepsis (EoS) occurs in the first 72 hours of age, whereas late-onset neonatal sepsis (LoS) occurs after the 72 hours of age. (Bulbul 2020) (Mehmet Satar 2012).

Causes of perinatal morbidity were as follows: sepsis (46.9%), patent ductus arteriosus (21.47%), respiratory distress syndrome (41.4%), and retinopathy. (Maryam Khoshnood Shariati 1 2015)

Antibiotic resistance rates are increasing globally for that, the World Health Organization (WHO) has recommended health care institutions to build up proper plans against antibiotic resistance, (WHO, Antimicrobial resistance 2023) Blood culture results are considered a keystone of antibiotic stewardship to direct targeted treatment and to decrease needless use of antibiotics. (Marie Chevallier 2017).

Our study aimed to analyze the blood culture results of preterm neonates in neonatal intensive care units (NICU), calculate the positivity rate, time of onset, spectrum of organisms, antimicrobial susceptibility pattern of these microorganisms, the risk factors associated with positive blood cultures and the development of the infection.

## 2. MATERIALS AND METHODS

### 2.1. Study Design, Period and Site

The study was designed as a retrospective epidemiologic analytical study all neonatal intensive care unit Al-

Hussein medical hospital at King Hussein medical center gestational age less than 37 weeks were included, we recorded all blood cultures for preterm during July 2018 to March 2019.

### 2.2. Inclusion criteria

Inclusion criteria were preterm neonates  $\leq 37$  weeks' gestational age.

### 2.3. Exclusion criteria

- A. Exclusion criteria were full term neonates.
- B. All stillbirths and all newborns with complex congenital heart disease were excluded.

### 2.4. Data collection

Data of positive blood cultures including identification of microorganisms and susceptibility pattern were obtained from Vitek 2 automated system reports in microbiology lab at princess Iman Center, we recorded the following demographic information; gender, gestational age, weight, age, length of hospital stay, and the use of (TPN) total parenteral nutrition.

### 2.5. Cultures

By using aseptic technique, all samples were collected, the drawn blood injected in Blood culture bottles containing a liquid formula that enhances microbial growth, then were send to department of microbiology to be incubated in one of detection systems (Versa Trek, Bactec and Bact alert).

If bottle flagged positive, by using gram stain technique the bottle was tested to mark the type of bacteria, Then the blood is sub cultured on to a blood, chocolate and mackonkey agar plate to isolate microbial colonies for full identification and antimicrobial susceptibility testing.

### 2.6. Antimicrobial susceptibility test

Antibiotic susceptibility was assessed for each family of organisms toward the following antibiotics Piperacillin-Tazobactam, Cefepime, Cefotaxime, Ceftazidime, Imipenem, Amikacin, Gentamicin, Ciprofloxacin, Septrin.

### 2.7. Ethical approval

An Institutional Review Board (IRB) approval was obtained from the ethical committee at Royal Medical Services.

Patient data privacy and confidentiality are maintained as this study was conducted in compliance with the ethical standards per Helsinki declaration.

## 3. RESULTS

### 3.1. Study population

Medical files at neonatal ICU wards were reviewed, 566 of neonatal were admitted to the neonatal ICU between January 2018 to March 2019.

Out of these 566 patients, 422 Neonates (74%) had less than 37 weeks, Of the 422 Neonates who had been less than 37 weeks, 76 Neonates (18%) were had bacteremia, of all premature with positive blood cultures.

EoNS and LoNS constituted (17, 22%) and (59, 78%), respectively with significant difference ( $p=.043$ ), Male: female ratio was 51%:49% respectively with no significant difference( $p=.132$ ), (60%) of premature less than 32 weeks developed bacteremia while (12%) of premature less than 28 weeks developed bacteremia.

Low birth weight was (44%), very low birth weight was (39 %), and extremely low birth weight (ELBW) were

(6%), The majority of the neonates had very low, moderately low, and extremely low birth weight (89%).

central line Presence was the important risk factor to increase bacteremia (90%) followed by the presence of endotracheal tube (84%), Mode of delivery for most of babies was C/S (76%) with significant deference( $p=.022$ ) (Table I).

The neonatal mortality rate in infants at less than 37 weeks was (16.6%), 46% of preterm deaths in infants less than 37 weeks old were caused by septicemias.

**Table I: Premature bacteremia: Clinical information and risk factors.**

Risk factors	All cases N= 422	Number of patients with sepsis No = 76 pts (18%)	LoNS 59 (78%)	EoNS 17 (22%)	P value .043
Male/female	220/202 (52%/48%)	39/37 (51%/49%)	30/29 (51%/49%)	9/8 (53%/47%)	.132
Gestational age < 37 weeks with bacteremia	76(18%)	76 (100%)	59 (78%)	17(22%)	.012
Gestational age<32 weeks	253 (60%)	45 (59%)	35 (59%)	4 (23%)	0.022
Gestational age<28 weeks	51(12%)	6(8%)	4(7%)	2(11%)	0.013
Extremely low birth weight (birth weight less than 1000 grams)	26(6%)	4(5%)	3(5%)	1(6%)	0.54
Very low birth weight (birth weight less than 1500 grams)	164 (39%)	29(39%)	20(34%)	9(15%)	0.041
low birth weight (birth weight less than 2500 grams)	185(44%)	34(45%)	25(43%)	9(52%)	.013
Mode of delivery CS/NVD	76%:24%	58/18 (76%/24%)	45/14 (77%/23%)	10/7 (59%/41%)	0.022
Central line	68(16%)	68(90%)	53(89%)	11(11%)	0.031
Mechanical ventilation	8(2%)	8(10%)	6(11%)	2(12%)	0.022
presence of endotracheal tube	64(15%)	64(84%)	50(85%)	14(15%)	0.011

### 3.2. Length of Stay (LOS)

The mean days of hospitalization was 6 days.

#### 3.2.1. Organisms causing neonatal sepsis

The organisms isolated in EoNS were (Coagulase negative Staphylococcus) CONS (8), Klebsiella pneumonia (1), Staphylococcus aureus (1), Enterobacter cloacae (1),Enterococcus faecalis (1) and Acinetobacter baumannii (1), Streptococcus agalactia (1), Bacillus spp (1), Streptococcus viridians (2), Likewise, the isolates of LONS were Acinetobacter baumannii (23), Klebsiella

pneumonia (10), Pseudomonas aeruginosa (1), CONS (12), E. coli (2), Enterobacter cloacae (2), Staphylococcus aureus (4), Enterococcus spp. (1), Streptococcus pneumonia (1), Streptococcus viridians (3). (Table 2)

Gram negative bacteria is the most common causes of bacteremia in this study (56%), Acinetobacter baumannii (31%) and Klebsiella pneumonia (15%) were the most common cause of gram-negative bacteremia. (Table 3)

**Table 2: Antibigram of blood culture isolates of Early and late onset neonatal sepsis.**

Antibiogram of blood culture isolates of Early onset neonatal sepsis (n=17 (22%))		Antibiogram of blood culture isolates of Late onset neonatal sepsis (n=59 (78%))	
Organism	Number (%)	Organism	Number (%)
CONS	8(47%)	Acinetobacter baumannii	24(39%)
Staph. Aureus	1(6%)	Klebsiella pneumonia	10(17%)

Enterococcus faecalis	1(6%)		Pseudomonas aeruginosa	1(1%)
Strep. Agalactia	1(6%)		CONS	12(20%)
Strep. Viridians	2(12%)		Enterobacter cloacae	2(3%)
Klebsiella pneumonia	1(6%)		Staphylococcus aureus	4(7%)
Acinetobacter baumannii	1(6%)		Enterococcus.	1(1%)
E. coli	1(6%)		Streptococcus pneumonia	1(1%)
Bacillus	1(6%)		Streptococcus viridians	3(5%)
			E coli	2(2%)

**Table 3: Distribution of gram-negative bacteria detected in blood cultures.**

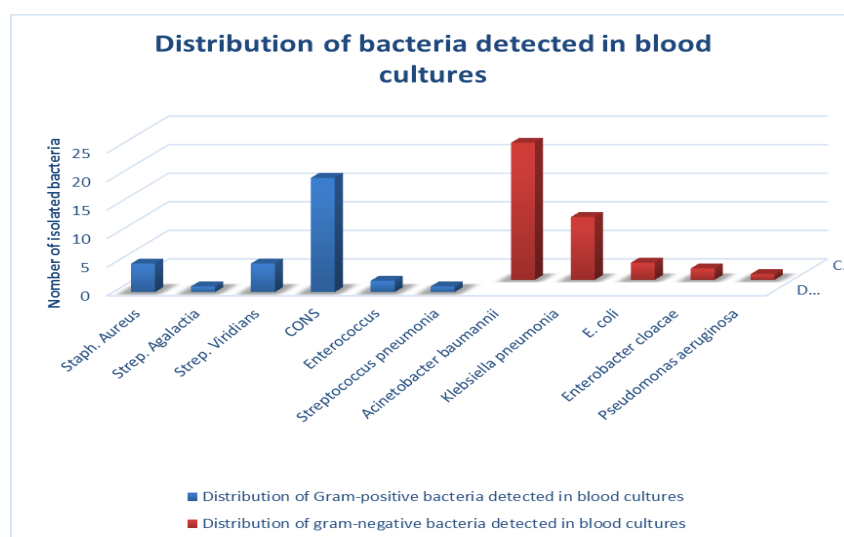
Pathogens	Number	Percentage related to all isolates (n=76)	Percentage related to gram negative isolates (n=42, 56%)
Acinetobacter baumannii	24	31%	56%
Klebsiella pneumonia	11	15%	26%
E. coli	3	4%	7%
Enterobacter cloacae	2	3%	5%
Pseudomonas aeruginosa	1	1%	2%

Gram positive bacteria was the most common causes of bacteremia in EoNS that causes 47% of infection, Staph. Aureus (15%), Strep. Viridians (15%), and CONS (58%)

were the most common cause of gram-positive bacteria. (Table 4 and Chart 1)

**Table 4: Distribution of Gram-positive bacteria detected in blood cultures.**

Pathogens	Number	Percentage related to all isolates (76)	Percentage related to gram positive isolates (34 ,44%)
Staph. Aureus	5	6%	15%
Strep. Agalactia	1	1.3%	3%
Strep. Viridians	5	6%	15%
CONS	20	26%	58%
Enterococcus	2	2.6%	6%
Streptococcus pneumonia	1	1.3%	3%

**Chart 1: Distribution of Gram-positive bacteria detected in blood cultures.**

**Table 5: Percentage of organisms detected in blood cultures.**

Pathogens	Total (76)
Gram negative bacteria	42(56%)
Gram positive bacteria	34(44%)

*Acinetobacter baumannii*, *Enterobacter cloacae*, and *Pseudomonas aeruginosa* were the three isolated bacterial families in the current investigation that ranged from 88% to 100% resistant to the majority of antibiotics.

#### 4.2. Antibiotic Susceptibility Pattern.

Table 6 and Chart 2 show the patterns of resistance of the bacterial isolates to empirical antibiotics often used in newborn infections. Ciprofloxacin should not be administered to young children, but applied to sepsis that has been culture proven to include germs resistant to other drugs.

*Acinetobacter baumannii* and *Enterobacter* were highly resistant to most antibiotics, Sceptin (100%), Ciprofloxacin (100%), Gentamicin (83%,100%

respectively), Amikacin (83%,100% respectively), Imipenem (92%,100% respectively), Ceftazidime (96%,100% respectively), Cefotaxime (96%,100% respectively), Cefepime (96%,100% respectively), Piperacillin-Tazobactam (96%,100% respectively).

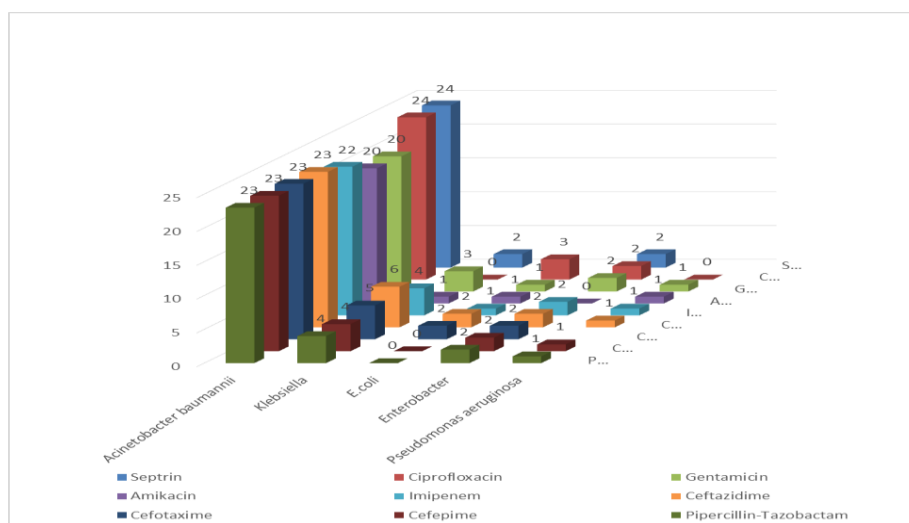
Imipenem was shown to have the highest sensitivity., Amikacin, Gentamicin and Piperacillin-Tazobactam. As seen in Table 6 and Chart 2, the studied antibiotic drugs' effects varied depending on the organism.

Cefepime and piperacillin-tazobactam were found to have a significant impact on *E. coli* isolates.

Sixty-two percent of the 26 isolates of Gram-negative bacteria had multidrug resistance (MDR).

**Table 6: Antibigram for the isolated against routinely used antibiotics (% resistant).**

Organism * Antibiotic resistance	# of isolates	Piperacillin-Tazobactam	Cefepime	Cefotaxime	Ceftazidime	Imipenem	Amikacin	Gentamicin	Ciprofloxacin	Septrin
<i>Acinetobacter baumannii</i>	25	23 (96%)	23 (96%)	23 (96%)	23 (96%)	22 (92%)	20 (83%)	20 (83%)	24 (100%)	24 (100%)
<i>Klebsiella</i>	11	4 (36%)	4 (36%)	5 (45%)	6 (54%)	4 (36%)	1 (9%)	3 (27%)	0	2 (18%)
<i>E. coli</i>	3	0	0	2 (66%)	2 (66%)	1 (33%)	1 (33%)	1 (33%)	3 (100%)	
<i>Enterobacter</i>	2	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	0	2 (100%)	2 (100%)	2 (100%)
<i>Pseudomonas aeruginosa</i>	1	1 (100%)	1 (100%)		1 (100%)	1 (100%)	1 (100%)	1 (100%)	0	

**Chart 2: Antibigram for the isolated against routinely used antibiotics (% resistant).**



## 5. DISCUSSION

Out of these 566 patients, 422 Neonates (74%) had less than 37 weeks and Male: female ratio was 51%:49% respectively with no significant difference ( $p=.132$ ), which was similar to previous study that found male female ratio was 52%:48% respectively and found (75%) of neonates admitted to the NICU was less than 37 weeks. (Woo Sun Song 2022)

76% of admitted Pts were delivered by cesarean section, our study is comparable to those of (Alaa Al Tawalbeh et al 2023), They reported the results of infants hospitalized to Prince Rashid bin Al-Hassan Hospital's NICU and came to the conclusion that the occurrence rate of confirmed neonatal sepsis was 12.5% of all neonatal admissions. Our research showed that 18% of neonates under 37 weeks who were admitted to the neonatal intensive care unit during that time had bacteremia, This increase in the percentage is because the sample in the first study included all neonatal admissions, while the second study included only preterm infants less than 37 weeks, high rates (49.9%) were reported in study in Egypt (Eman M. 2015), which explains the high standards of medical care provided in our hospital.

The newborn death rate for infants under 37 weeks in our study was 16.6%. that is similar to other study in Iran, The mortality rate for infants born before 32 weeks of gestational age was 15%. (Maryam Khoshnood Shariati M.D. 2015), 46% of preterm deaths in infants less than 37 weeks old were caused by septicemias, which was less than previous study that found mortality rate was 51% in Pts with septicemias (Khaled Salama 2021), On the other hand, a higher mortality rate (8.7%) among admitted neonates was reported by (Sivasubramaniam et al. in 2015) at Al-Bashir Hospital. In parallel, neonatal mortality 12% of all births in Jordan was found by (Batieha et al. in 2016).

The reported incidence varies, the wide variability can be contributed to the differences in socioeconomic levels, perinatal and neonatal care facilities, infection control protocols, and antibiotic use (S Vergnano 2005) In the neonates under 37 weeks in our study, the neonatal death rate was 16.6%.

That is similar in other study in Iran, Infants born before 32 weeks of gestational age had a 15% death rate. (Maryam Khoshnood Shariati M.D. 2015).

In our study the Gram-negative bacteria was the most common causes of bacteremia (56%) which was similar to previous study that found Gram-negative bacilli constituted the majority of isolated organisms 62%. (Khaled Salama 2021), our study is comparable to those of (Alaa Al Tawalbeh et al 2023), With 62% and 60% of all positive cultures, respectively, the acquired Gram-negative bacteria were the primary microbial isolates causing infection in both EOS and LOS.

Gram positive bacteria was the most common causes of bacteremia in EoNS that causes 47% of infection, Staph. Aureus (15%), Strep. Viridians (15%), and CONS (58%) were the most common cause of gram-positive bacteria, Gram negative bacteria is the most common causes of bacteremia in this study (56%), Acinetobacter baumannii (31%) and Klebsiella pneumonia (15%) were the most common cause of gram-negative bacteremia, this is Compatible with A constituted 69% of sepsis CoNS organisms MDR and retrospective review from Jordan reported that Klebsiella episodes in NICU. (S Vergnano 2005)

### 5.1 Antibiotic susceptibility pattern

Acinetobacter baumannii and Enterobacter were highly resistant to most antibiotics, Sceptin (100%), Ciprofloxacin (100%), Gentamicin (83%, 100% respectively), Amikacin (83%, 100% respectively), Imipenem (92%, 100% respectively), Ceftazidime (96%, 100% respectively), Cefotaxime (96%, 100% respectively), Cefepime (96%, 100% respectively), Piperacillin-Tazobactam (96%, 100% respectively) this result was similar to previous study that showed highest resistance to ampicillins, cephalosporins, and piperacillin-tazobactam (Khaled Salama 2021)

Best sensitivity was observed to imipenem, Amikacin, Gentamicin and Piperacillin-Tazobactam. The studied antibiotic drugs' effects varied depending on the organism. It was discovered that Cefepime and Piperacillin-Tazobactam had a significant impact on E. coli isolates, and that 26 isolates of Gram-negative bacteria (62%), exhibited Multidrug Resistance (MDR).

which was similar to previous study that found the best sensitivity was observed with imipenem and even though all strains of Acinetobacter were highly resistant to quinolones, 29.5% of them were imipenem-sensitive. (Eman M. 2015)

LOS accounted for 78% of newborn sepsis, whereas EOS was linked to 22%. Furthermore, the newborn sepsis occurrence that was collected cannot be compared to the study conducted by (Shehab El-Din et al. 2015), who gave the EOS and LOS occurrence rates, which were 55% and 45%, respectively. In addition, which was similar to previous study (Al-Matary et al. 2019) According to a study conducted in King Fahad Medical City, the likelihood of newborn sepsis among all positive cases was 88% at LOS and 12% at EOS.

Compared to other documented hospitalization times of 5.5 to 12.5 days, the median length of bacteremia was 5 to 12 days, and the primary length of stay was 6 days, (Wasim Khasawneh 2020).

Most of the newborns (89%), had birth weights that were very low, moderately low, and extremely low birth

weight, this is compatible with other study (90.6%) (Khaled Salama 2021)

## 6. Prevention

The Pediatric Infectious Diseases Society (PIDS), National Institute for Health and Care Excellence (NICE), and Infectious Diseases Society of America (IDSA) have recommended preventable measures to reduce infection and better management of invasive procedures within NICU.

- 1- Hand hygiene-based alcohol sanitizer before and after patient contact is effective and efficient against many microorganisms.
- 2- Lactoferrin, phagocytes, secretory antibodies, and prebiotics found in breast milk from mothers enhance host defense and gastrointestinal function and are linked to a decreased risk of infection outbreaks and neonatal sepsis.
- 3- Proper management and safe procedure of Total Parenteral Nutrition (TPN) according to the guidelines of (IDSA), (PIDS) and (NICE) should be strictly followed by healthcare providers in NICU.
- 4- Ongoing instruction and training for medical staff on the use of intravascular catheters and correct insertion techniques, sterilization, and update infection control guidelines have been widely recommended.

## 7. Limitation of study

Our study is single-center study performed at NICU in Al-Hussein medical hospital at King Hussein medical center.

## 8. CONCLUSION

Of all preterm newborn admissions to the NICU, 13% had neonatal sepsis, comprising higher proportion of LOS (78%), In both EOS and LOS, the most frequent species found were CoNS and Acinetobacter baumannii, respectively., the 3 isolated bacterial families (Acinetobacter baumannii, Enterobacter cloacae, Pseudomonas aeruginosa) were from 88% to 100% resistant to most antibiotics, Bacteremia was most frequently caused by gram-negative bacteria (56%). In EoNS, gram-positive bacteria were the most frequent cause of bacteremia, accounting for 47% of infections.

## 9. Abbreviations

CoNS: coagulase-negative staphylococci

EoNS: Early-onset neonatal sepsis

LoNS: Late onset neonatal septicemia

ELBW: Extremely low birth weight

MD: medicine doctor

Gestational G:

ELBW: extremely low birth weight

WHO: World Health Organization

Caesarean section S:C

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