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Identification of bacterial pathogens and antimicrobial susceptibility of early-onset sepsis (EOS) among neonates in Palestinian hospitals: a retrospective observational study

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Abstract

Background Early-onset sepsis (EOS) remains a significant cause of morbidity and mortality in neonates worldwide, particularly in low-income countries. Identification of causative bacterial pathogens and assessment of their antimicrobial susceptibility are essential for guiding appropriate therapy and improving outcomes. The aim of this study was to determine the incidence, bacteriological profile and antibiotic susceptibility patterns of culture-positive EOS among a cohort of neonates in the Occupied Palestinian Territories (oPt).

Methods This retrospective observational study was conducted on neonates with proven positive blood cultures or positive cerebrospinal fluid (CSF) admitted to eight neonatal intensive care units (NICU) in the West Bank, oPt between January 2017 and December 2019. Data on microbiology laboratory blood cultures were retrieved from NICU registers and medical records were reviewed to obtain data on mothers and neonates.

Results Among the 95,319 neonates admitted to the eight NICUs during the study period, we detected 292 neonates with culture-proven EOS, resulting in an incidence rate of 3 per 1000 live births.

The most common gram-positive bacteria identified among neonates were α *hemolytic streptococcus (11.6%), CoNS* (11.3%), and *GBS* (8.6%). *E. coli* (15.1%) and *Klebsiella spp.* (15.1%) were the most common gram-negative bacteria, followed by *Acinetobacter* (7.9%). Findings revealed gram-positive organisms were resistant to ciprofloxacin (57.1%) and highly sensitive to vancomycin (97.9%), meropenem (89.2%), amikacin (82.6%) and Piperacillin-Tazobactam (82.4%). Gram-negative organisms showed the highest antibiotic resistance to ampicillin (87.2%), cetofaxime, and highest sensitivity to meropenem (82.0%), Piperacillin-Tazobactam (70.7%), and amikacin (66.4%).

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Conclusion Our findings underscore the importance of continuous surveillance of bacterial pathogens and their antimicrobial susceptibility patterns in the management of EOS among neonates in Palestinian hospitals. The findings generated will guide clinicians in selecting appropriate empirical therapies and facilitating early and targeted interventions. Future research should focus on strategies to enhance infection prevention and control measures in Palestinian neonatal care unites to mitigate the burden of EOS and antimicrobial resistance.

Keywords Antibiotic susceptibility, Early-onset sepsis, Neonates, Bacterial pathogens, Gram-positive, Gram-negative

Introduction

Neonatal sepsis refers to an infection involving bloodstream in newborn infants less than 28 days old. It is divided into early-onset sepsis (EOS) or late-onset sepsis (LOS) based on the age of presentation after birth with different experts using 72 h or seven days as the cutoff [1]. According to the World Health Organization (WHO), four million newborns die each year globally during the first four weeks after birth. Of these, 75% die prematurely during the first week of life [2]. The major causes of neonatal deaths globally are attributed to infections (neonatal sepsis, meningitis, and pneumonia) (35%), preterm births (28%), intrapartum-related complications (24%), and asphyxia (23%). EOS and LOS are the leading causes of neonatal morbidity and mortality globally and are responsible for 30–50% of the total neonatal deaths each year in developing countries [3]. Estimates of the incidence of EOS among neonates range from 0.54 to 1.19 per 1,000 live births [4–6] or 9 to 12 per 1,000 neonatal intensive care unit (NICU) admissions [7, 8].

Most EOS infections are a result of vertical transmission of bacteria from colonized mothers to neonates during the intrapartum period. Previously, the most common pathogen causing EOS in neonates was *Streptococcus agalactiae* also referred to as *Group B* Streptococcus (*GBS*) [9]. However, more recently, *Escherichia coli* (*E. coli*) has become the most common cause, followed by *GBS* [4, 10]. Emergence of antimicrobial resistance has become a global concern. Organizations worldwide have been collaborating for more than 20 years to provide recommendations for the use of intrapartum antibiotic prophylaxis (IAP) to prevent EOS. A previous cohort study in Canada reported a significant decrease in *GBS* and revealed *GBS* was more common in term infants and *E. coli* was more common in preterm infants [11]. These findings were in line with other studies in the USA and Italy, which also showed a trend of increased EOS caused by *E. coli* that was most pronounced in preterm neonates [4, 5, 10, 12]. Continued surveillance of EOS epidemiology is especially important in light of recent debate on the continued utility of ampicillin and gentamicin for empirical coverage. In previous studies, up to 1 in 10 *E. coli* isolates causing neonatal EOS were resistant to both ampicillin and gentamicin [13]. Although the regimen provides adequate coverage for *GBS*, because this organism remains almost universally sensitive to ampicillin, there is concern about increasing prevalence of EOS infections due to organisms besides *E. coli* and *GBS*, including other multidrug-resistant Gram-negative bacteria [14].

There is a crucial need to understand the current early-onset neonatal sepsis (EONS) epidemiology. With a limited reserve of antibiotics, increasing antimicrobial resistance has become a great challenge in the management of neonatal sepsis. Knowledge of prevalent bacterial pathogens and their antibiotic susceptibility pattern is crucial when choosing the appropriate empirical therapy in order to decrease morbidity and mortality. Ongoing surveillance of EOS is critical to optimize prevention and treatment strategies.

To the best of our knowledge, this is the first national study in the Occupied Palestinian Territories (oPt) to assess the incidence of EOS and the epidemiological patterns such as its causative organisms as well as their antibiotic susceptibility patterns. The aim of this study is to determine the incidence, clinico-bacteriological profile and antibiotic susceptibility pattern of culture-positive EOS among a cohort of neonates and to identify the main risk factors of EOS among neonates delivered in eight major NICUs in the oPt.

Methods

Study design, setting and population

This is a retrospective observational study conducted on neonates admitted to eight major neonatal departments in the West Bank and East Jerusalem, oPt, including Alia Hospital, Caritas Hospital, Holy Family Hospital, Makassed Hospital, Palestine Medical Complex (PMC), Palestine Red Crescent Society-Jerusalem Hospital, Palestine Red Crescent Society-Hebron Hospital, and Rafidia Hospital. Neonates admitted to the NICUs between January 2017 and December 2019 with proven positive blood cultures or positive cerebrospinal fluid (CSF) cultures in the first seven days after birth were included in the study, according to the clinical status of baby. The inclusion criteria were as followed: 1) infants younger than seven days post-partum; 2) with positive blood culture or positive CSF culture from lumbar puncture; and 3)

neonatal clinical data and mother's obstetric data could be accessed. Term Neonates with only one positive blood culture or CSF culture of *Coagulase negative staphylococci* (*CoNS*), no indwelling intravascular catheters and did not have any symptoms of sepsis were excluded due to the possibility of contamination during sample handling. Neonates were also excluded if they had positive blood cultures for multiple organisms or a positive CSF culture as a result of drain, reservoir, shunt or an intracranial surgical procedure. In this study, EOS was defined as sepsis occurring within the first seven days of life. Ethical approval was obtained from Hospital Administration at the Palestine Ministry of Health and the administration of each hospital included in the study. Permission to access medical records of neonates and their mothers was obtained from the hospital director at each hospital.

Data collection

For data collection, microbiology laboratory blood culture registers were reviewed and all blood culture positive neonates were identified. Medical records were subsequently evaluated and data for mothers and neonates were obtained. Maternal characteristics collected include socio-demographics (age, residency, gravida, para, abortion) of mothers, delivery mode, and maternal risk factors: preterm rupture of membranes (ROM), prolonged ROM (Prolonged ROM > 18 h prior to delivery), maternal urinary tract infection (UTI), maternal *GBS* status, *GBS* UTI, maternal fever (intrapartum maternal temperature ≥ 38°C), maternal white blood count (WBC), clinical diagnosis of chorioamnionitis, and Apgar score at one minute/five minutes. Neonatal characteristics collected include gestational age (GA) at birth, neonate birth weight, age at presentation, congenital anomalies, surgical procedures, central line/umbilical venous catheter (UVC)/peripherally inserted central catheter (PICC) placement before sepsis, and family history (previous sibling with neonatal death/neonatal sepsis). Information on laboratory parameters including WBCs, neutrophils, platelet count, CRP level at the time of the taking blood culture, and chest x-ray were obtained. In addition, clinical signs of sepsis (lethargy, jaundice, hyperthermia, hypothermia, seizures, apnea, feeding intolerance, hypo/hyper-tonia, shock, hypo-perfusion prior to infection were obtained. Data on blood culture isolated species of causative organisms and their susceptibility, CSF culture, and the organism isolated from CSF culture were retrieved. The interval between taking blood culture and positive blood culture was calculated to try to explain whether the growth is a true infection or contamination, particularly for *CoNS* as any growth which lasts more than 24 h is considered contamination [15, 16]. In this study, according to the site of infection, EOS was classified as primary blood stream infection (PBSI) or meningitis. The diagnosis of meningitis was established for patients who presented with a positive CSF culture. *CoNS*, was considered as an EOS agent, due to time of early positivity (< 24 h) of the cultures [17], and for having been associated to a compatible clinical process and unspecific altered laboratory examinations. *CoNS* is widely recognized as a contaminant in otherwise healthy term neonates who have not undergone invasive procedures [18]. *Micrococci, Propionibacteria, Corynebacteria, or Diphtheroids, Bacillus* were considered contaminants, regardless of site determination of contaminant status. Cultures that grew more than one organism were considered contaminants on the basis of the attending physician's judgment and decision.

Blood culture and antimicrobial sensitivity tests

The hospitals in the present study followed standard international microbiological techniques. Blood cultures are the gold standard test for the diagnosis of blood stream infection and should be performed in all cases of suspected sepsis prior to administration of antibiotics. Accordingly, blood cultures were taken from neonates with suspicious sepsis and any premature baby less than 34 weeks with preterm labor, pre labor rupture of membrane, or any concern of intra-amniotic infection and if indication for *GBS* prophylaxis and inadequate *GBS* intrapartum antibiotics was taken. Under aseptic techniques blood samples were collected. Nurses conducted a blood culture in accordance with institutional protocols, utilizing sterile gloves throughout the procedure. They also prepped a skin area of about 5 cm in diameter at the intended venipuncture site. This area was cleansed thoroughly with 70% isopropyl alcohol, followed by povidone-iodine, and followed again by alcohol. The skin was allowed to dry for at least 1 min before venipuncture. One-mL sample of blood was drawn from a fresh venipuncture site and added to a bottle containing 5–10 mL of blood Agar culture media. The blood cultures were incubated aerobically at 37°C and observed daily for consecutive three days for preliminary results by checking the presence of one of the following findings on culture media: air bubbles (gas production), and coagulation of broth. At the same time, subcultures were made during three successive days on enriched and selective media including blood agar, chocolate agar, MacConkey agar plates and examined for growth after 24–48 h of incubation. Showing no growth on the 7th day, blood cultures were reported as sterile. Isolated bacteria were identified using different standard techniques like Gram stain reaction, biochemical reaction properties (Lactase, Catalase, Indolase), morphological and colony characteristics. Antimicrobial susceptibility test (AST) was carried out

Table 1 Characteristics and clinical profile of mothers of neonates with EOS

Variable	Category	N	(%)
Socio-demographics			
Residence, (*N* = 180)	City	92	51.1%
	Village	84	46.7%
	Camp	54	2.2%
Maternal age of mother (years), (*N* = 148)	< 20	10	6.8%
	20–30	101	68.2%
	31–40	36	24.3%
	> 40	1	0.7%
Maternal characteristics			
Gravida, (*N* = 234) (mean, SD)	3.2 ± 2.3		
Para, (*N* = 233) (mean, SD)	2.5 ± 2.0		
Abortion, (*N* = 234) (mean, SD)	0.43 ± 1.1		
GBS status (*N* = 32)	Negative	20	6.9%
	Positive	12	4.1%
Maternal UTI, (*N* = 180)	Yes	21	7.2%
	No	159	54.6%
GBS UTI, (*N* = 171)	Yes	1	0.3%
	No	170	58.4%
Prolonged ROM (Prolonged ROM > 18 h prior to delivery), (*N* = 291)	Yes	45	15.5%
	No	223	76.6%
Preterm ROM, (*N* = 199)	Yes	64	21.9%
	No	135	46.2%
Elevated maternal temperature > 38ºC (after onset of labor), (*N* = 247)	Yes	13	4.5%
	No	234	80.1%
Elevated maternal WBC (WBC > 10,000, after onset of labor), (*N* = 141)	Yes	30	10.3%
	No	111	38.0%
Clinical diagnosis of chorioamnionitis, (*N* = 246)	Yes	9	3.1%
	No	237	81.2%
Maternal antibiotics (GSB prophylaxis given), (*N* = 215)	Yes	25	8.6%
	No	190	65.1%

GBS Group B Streptococcus, *ROM* rupture of membrane, *UTI* urinary tract infection, *WBC* white blood count

by Kirby–Bauer disc diffusion method using special agar with incubation of 24 h at 37°C [19] and susceptibility patterns were determined following Clinical Laboratory Standard Institute standards (CLSI) guidelines [20].

Data analysis

The incidence rate of EOS was determined per 1000 live births. The microbiology of EOS was determined by using proportions of bacterial pathogens overall and by Gram-positive or Gram-negative pathogen status. Data were analyzed using descriptive statistics methods: categorical variables were expressed by absolute and relative frequencies (%) and continuous variables expressed as means and standard deviations. For the statistical analysis of data, we used STATA, version 16 (USA).

Results

General characteristics and clinical profile of neonates and mothers

This retrospective observational study of 95,319 neonates identified 332 neonates with culture proven EOS which were admitted to the respective eight NICUs. Among the 332 neonates with EOS, 40 (12.0%) had blood cultures which were identified as contaminated, and thus were excluded from the analysis. The total sample included in the study analysis is 292 neonates. Table 1 presents the main characteristics and clinical profile of mothers of neonates with EOS. Due to incomplete medical records at study sites, there was missing data for most mothers.

Among the mothers which had records available at the study sites, 45 (15.5%) of mothers had prolonged ROM, and 64 (21.9%) had preterm ROM. Among the mothers

of neonates, nine (3.1%) had a clinical diagnosis of chorioamnionitis, and 25 (8.6%) were given GBS prophylaxis. Among the 32 mothers which were tested for *GBS* colonization, 12 (4.1%) tested positive (Table 1).

In terms of neonate characteristics, 172 (60.6%) of the neonates were male and 110 (38.1%) were delivered between weeks 28–34. The mean age at presentation (days) among all neonates was 2.4 ± 1.9 (N = 254). A total of 144 (49.3%) of neonates were delivered by normal vaginal delivery (NVD) and 143 (49.0%) were delivered by cesarean section (CS).

In terms of the laboratory characteristics, among the neonates which had records available, chest x-rays were taken for 260 (81.8%) of neonates and pneumonia was present among 56 (24.3%) of neonates. The mean age of neonates when blood culture was taken was 2.9 days, and the mean age of neonates when blood culture was positive is 4.5 days. CSF cultures were taken for 104 (35.6%) of neonates (Table 2).

Incidence of early-onset neonatal sepsis (EOS)

In this study, 95,319 newborns were delivered in the study hospitals from January, 2017 to December, 2019. Of the total newborns, 292 neonates had EOS for an incidence rate of 3 per 1000 live births.

Bacteriological profile and infection rates

Among the 292 neonates included in the analysis, 282 (96.6%) PBSI cases including one fungal infection and one unknown bacteria; 14 (4.8%) meningitis cases and 56 (24.3%) cases of pneumonia were identified among neonates.

The most common gram-positive bacteria identified among neonates were α *hemolytic streptococcus (11.6%), CoNS* (11.3%), *GBS* (8.6%), *Staphylococcus Aureus* (S. Aureus) (6.9%), and *Enterococcus species* (5.2%) (Table 3). The incidence of *GBS* in this study is 0.26 per 1000 live births. *E. coli* (15.1%) and *Klebsiella spp.* (15.1%) were the most common gram-negative bacteria, followed by *Acinetobacter* (7.9%) and *Enterobacter species* (4.5%) (Table 3). Findings showed the majority of blood cultures identified such as *α-hemolytic streptococcus* (10.2%), *E. coli* (9.2%) and *GBS* (7.5%) bacterial cases were taken within the first 72 h after birth (Table 3).

Causative organisms of EOS in term and preterm neonates and by birth weight status

Findings show the incidence of EOS among preterm infants is 1.9 per 1000 live births while the incidence of EOS among term infants is 1.1 per 1000 live births. Table 4 presents a comparison of the causatives organisms of EOS among this sample of preterm and term infants, as well as across different birth weight categories: extremely low birth weight (ELBW), low birth weight (LBW), and normal birth weight (NBW). Among the Gram-positive bacteria, *CoNS* was predominantly found in preterm (87.9%) and LBW (54.6%) infants, while *α-hemolytic streptococcus* was more common in preterm (58.8%) and NBW (67.7%) neonates. *GBS* was most frequently found in term (68.0%) and NBW (80.0%) infants. For Gram-negative organisms, *E. coli* and *Klebsiella spp.* are significantly more prevalent in preterm (72.7% and 84.1%, respectively) and LBW (59.1% and 68.2%) infants, showing a lower occurrence in term neonates. Likewise, *Acinetobacter* exhibited a higher incidence in preterm and LBW groups (Table 4). The distribution of causative organisms of EOS varies significantly by neonatal characteristics, emphasizing the importance of stratified clinical approaches and targeted antimicrobial therapies based on gestational age and birth weight.

Antibiotic susceptibility

Table 5 shows the pattern of antibiotic susceptibility of gram-positive causative organisms of EOS. Findings revealed gram-positive organisms were resistant to ciprofloxacin (57.1%). However, the same species showed the highest sensitivity to vancomycin (97.9%), meropenem (89.2%), amikacin (82.6%) and Piperacillin-Tazobactam (82.4%) (Table 5). Particularly, GBS was found to be 94% sensitive to ampicillin, α hemolytic strep was 54% sensitive to ampicillin and 91% sensitive to cefotaxime and 100% of CoNS cases were sensitive to vancomycin.

Gram-negative organisms showed the highest antibiotic resistance to ampicillin (87.2%), highest sensitivity to meropenem (82.0%), Piperacillin-Tazobactam (70.7%), and amikacin (66.4%) (Table 6). Among the most common organisms identified, *E. coli* showed the highest sensitivity to meropenem (100%), amikacin (97.0%), gentamycin (68.0%), and cefotaxime (58.0%), and resistant to ampicillin (92.0%). *Klebsiella spp.* were highly resistant to ampicillin (100%), cefotaxime (82.0%) and gentamycin (76.0%) and showed sensitivity to meropenem (87.5%) and amikacin (65.0%). In addition, our findings showed Acinetobacter was highly resistant to cefotaxime (100%), and resistant to amikacin (85.7%), gentamycin (78.5%), and meropenem (76.0%).

Neonatal and maternal risk factors associated with EOS

Prematurity and LBW were the top neonatal risk factors of EOS. Among all neonates with EOS in this study, 183 (63.3%) were preterm babies (GA: < 37 weeks); 170 (58.2%) had LBW (< 2500gms); and 14 (4.8%) neonates had an Apgar score ≤ 5. Approximately, 64 (21.9%) of mothers with preterm ROM, 13 (4.4%) had a history of maternal fever, 21 (7.2%) had a UTI and 45 (15.4%) of mothers with prolonged ROM had babies with EOS. In

Table 2 Characteristics and clinical profile of neonates with EOS, (*N* = 292)

Variable	Category	(N)	(%)
Neonate characteristics			
Gender, (*N* = 284)	Female	112	39.1%
	Male	172	60.6%
GA at birth (weeks), (*N* = 289)	< 28	37	12.5%
	28–34	110	38.1%
	35–37	36	12.5%
	> 37	106	36.7%
Mode of delivery, (*N* = 290)	IVD	3	1.0%
	NVD	144	49.3%
	CS	143	49.0%
APGAR score at 1 min, (*N* = 286)	≤ 5	70	24.0%
	> 5	216	74.0%
APGAR score at 5 min, (*N* = 286)	≤ 5	14	4.8%
	> 5	272	93.2%
Birth weight (grams), (*N* = 292)	< 1000	28	9.7%
	1000–2500 g	136	46.9%
	2501–4000 g	121	41.7%
	> 4000	3	1.0%
Age at presentation (days), (*N* = 254) (mean, SD)	2.4 ± 1.9		
Feeding, (*N* = 215)	NPO	109	37.3%
	Breast	64	21.9%
	Formula	42	14.4%
Congenital anomalies, (*N* = 272)	Yes	30	10.3%
	No	242	82.9%
Surgical or other invasive procedures before sepsis, (*N* = 292)	Yes	21	7.2%
	No	371	92.8%
Central Line for neonate, (*N* = 332)	Yes	104	35.6%
	No	188	64.4%
Family History			
Previous sibling/s with neonatal death(s), (*N* = 252)	Yes	9	3.1%
	No	243	83.2%
Previous sibling/s with neonatal sepsis, (*N* = 183)	Yes	1	0.3%
	No	176	60.3%
Clinical signs of Sepsis			
Lethargy, (*N* = 332)	Yes	132	45.2%
	No	160	54.8%
Jaundice, (*N* = 332)	Yes	150	51.4%
	No	142	48.6%
DIC, (*N* = 331)	Yes	80	27.4%
	No	211	72.3%
Hyperthermia/Hypothermia, (*N* = 331)	Yes	42	14.4%
	No	248	85.2%
Seizures, (*N* = 331)	Yes	10	3.4%
	No	281	96.2%
Apnea, (*N* = 332)	Yes	120	41.1%
	No	172	58.9%
Feeding Intolerance, (*N* = 331)	Yes	94	32.2%
	No	197	67.5%

Table 2 (continued)

Variable	Category	(N)	(%)
Hypotonia, (*N* = 332)	Yes	38	13.0%
	No	254	87.0%
Hypertonia, (*N* = 332)	Yes	8	2.7%
	No	284	97.3%
Shock, (*N* = 331)	Yes	67	23.0%
	No	263	76.7%
Laboratory Investigation			
Chest x-ray, (*N* = 278)	Yes	223	76.4%
	No	55	18.8%
Pneumonia present, (*N* = 223)	Yes	56	24.3%
	No	166	72.2%
	Pneumothorax	1	0.4%
Age blood culture was drawn (days) (*N* = 262) (mean, SD)	2.9 ± 2.0		
Age blood culture was positive, (*N* = 252) (mean, SD)	4.5 ± 2.2		
CSF culture taken, (*N* = 282)	Yes	104	35.6%
	No	178	61.0%
WBCs, (*N* = 287)	< 5000	51	(17.8%)
	5000–30000	216	(75.3%)
	> 30000	20	(7.0%)
Neutrophils, (*N* = 285)	< 1500	40	(14.0%)
	> 1500	245	(86.0%)
Platelets count, (*N* = 288)	< 50000	30	(10.4%)
	50000–100000	40	(13.9%)
	> 100000	218	(75.7%)
CRP, (*N* = 292)	< 6	115	(39.4%)
	≥ 6	187	(60.6%)
If LP done, WBCs in CSF, (*N* = 82)	< 30	71	(86.6%)
	≥ 30	11	(12.0%)

CRP C-reactive protein, *CS* caesarean section, *CSF* cerebrospinal fluid, *DIC* Disseminated intravascular coagulation, *GA* gestational age, *IVD* Induced vaginal delivery, *LP* lumbar puncture, *NVD* normal vaginal delivery, *NPO fasting, WBC* White blood count

addition, 30 (10.3%) mothers had maternal WBC > 10, and among the 32 mothers which were tested for *GBS* colonization, 12 (4.1%) tested positive. Overall, 75.3% of all neonates had at least one risk factor and 32.5% of neonates had three or more risk factors.

Discussion

This retrospective study assessed the frequency of bacterial pathogens, conferred the antibiotic susceptibility patterns and analyzed the main risks of EOS of the common bacterial pathogens of neonatal sepsis in Palestine. The study findings present the clinical and microbiological data of neonates with positive blood cultures. The incidence of EOS in this study is 3 per 1000 live births, fairly higher than findings in another study conducted among Arab states in the Gulf region, which found an incidence ranging from 0.54 to 2.64 per 1000 live births among neonates [21] and another prospective study conducted in Jordan [22] which found an incidence of 2 per 1000 live births for EOS. In contrast, the incidence of EOS in this study was lower than that of another study conducted in Egypt which found an incidence of 4 per 1000 live births [23]. These variations in incidence rates of EOS in different studies could be due to differences in culture-techniques and study designs.

Globally, sepsis remains one of the major causes of morbidity and mortality in neonates, in spite of recent advances in NICUs [24]. The major burden of the problem occurs in the developing world while most evidence is derived from developed countries. The rates of PBSI in neonates are 3–20 times higher in developing countries [25]. Neonatal sepsis related mortality is largely preventable with prevention of sepsis itself, timely recognition, and proper antimicrobial therapy [26].

In developed countries, the number of patients with EOS has decreased throughout the past decades, and

Table 3 Microbiology of EOS: Distribution of Gram-positive and Gram-negative Organisms, by blood cultures taken within one week of birth and within 72 h of birth, (*N* = 292)

Organism	Blood culture taken within 1 week of birth N (%)	Blood culture taken within 72 h of birth N (%)
Gram-positive bacteria (total)	**146 (50.0%)**	
Streptococcus		
a hemolytic streptococcus ***(3 meningitis cases)***	37 (11.6%)[a]	30 (10.2%)
GBS ***(2 meningitis cases)***	25 (8.6%)	22 (7.5%)
streptococcus pyogenes ***(1 meningitis cases)***	4 (1.0%)[a]	2 (0.7%)
Enterococcus species	15 (5.2%)[a]	11 (3.8%)
Staphylococcus		
CoNS	33 (11.3%)	3 (1.0%)
Staphylococcus Aureus ***(4 meningitis cases)***	24 (6.9%)[a]	14 (4.8%)
MRSA	7 (2.4%)	4 (1.4%)
Listeria	1 (0.3%)	1 (0.3%)
Gram-negative bacteria (total)	**144 (49.4%)**	
E. coli ***(1 meningitis case; 11 ESBL-E. coli cases)***	44 (15.1%)[a]	27 (9.2%)
Pseudomonas species	6 (2.1%)	2 (0.7%)
Klebsiella spp. ***(12 ESBL cases, 5 CRE cases, 5 Klebsiella spp. multidrug resistant cases)***	44 (15.1%)	19 (6.5%)
Acinetobacter	23 (7.9%)	9 (3.1%)
Enterobacter species ***(1 meningitis case)***	14 (4.5%)[a]	5 (1.7%)
Yersinia enterocolitica	1 (0.3%)	1 (0.3%)
Proteus ***(1 meningitis case)***	1 (0.3%)[a]	-
Serratia	3 (1.0%)	2 (0.7%)
Haemophilus influenza ***(1 meningitis case)***	6 (1.7%)[a]	3 (1.0%)
Morganella	1 (0.3%)	-
Stenotrophomons maltophila	1 (0.3%)	1 (1.0%)
Unknown bacteria	**1 (0.3%)**	-
Fungal Infection		
Candida albicans	**1 (0.3%)**	-

CoNS Coagulase negative staphylococci, *MRSA* Methicillin-resistant Staphylococcus aureus, *GBS* Group B streptococcus, *S. Aureus* Staphylococcus Aureus

[a] Include Meningitis cases

α hemolytic streptococcus meningitis cases could be contaminated

much of that is owed to the use of IAP at the time of birth. This association was demonstrated previously, in a multicenter study by Chan et al., who showed a decrease in incidence of EOS (3.25 versus 2.26 per 1000 live births), after the implementation of GBS screening and IAP [27], and has been widely illustrated in recent neonatal sepsis literature [26, 28].

It is recognized globally that *GBS* and *E. coli* are the most common causes of early -onset sepsis, accounting for approximately two-thirds of early onset infections [29]. Recent reports have demonstrated a changing epidemiology of EOS, with a reduction in cases caused by *GBS* and a relative increase in cases caused by *E. coli* [4, 30, 31]. It remains unclear if the incidence of *E. coli* EOS is actually increasing due to factors such as IAP [31], or if it is attributable to advancements in neonatal resuscitation that have resulted in greater survival of preterm infants [4]. Owing to the causative agents that vary from region to region and the emergence of antibiotic resistance, knowledge of prevailing organisms in the local environment of an NICU and their antibiotic sensitivity pattern according to periodic surveys are essential for realizing effective treatment and favorable outcomes [31, 32].

In this study, among 292 isolated pathogens, *E. coli* and *Klebsiella spp.* were the most commonly isolated pathogens, a finding similar to other studies in Canada [31], the United States of America (USA) [4] and Saudi Arabia [33]. Similarly, Pokhrel et al. [34] and Shrestha S et al. [35], and Almohammady et al. [36] showed

Table 4 Distribution of causative organisms by term and preterm neonates and by birth weight status, (*N* = 292)

Causative organisms	Pre-term (< 37 weeks) (*N* = 186)	Term (> 37 weeks) (*N* = 96)	ELBW (*N* = 31)	LBW (*N* = 139)	NBW (*N* = 122)
Gram-positive bacteria					
CoNS	***29 (87.9%)***	***4 (12.1%)***	***11 (33.3%)***	***18 (54.6%)***	***4 (12.1%)***
a hemolytic streptococcus	***20 (58.8%)***	***14 (41.2%)***	***1 (2.9%)***	***10 (29.4%)***	***23 (67.7%)***
GBS	**8 (32.0%)**	**17 (68.0%)**	**0 (0.0%)**	**5 20.0%)**	**20 (80.0%)**
Staphylococcus Aureus	**5 (25.0%)**	**15 (75.0%)**	**2 (10.0%)**	**5 (25.0%)**	**13 (65.0%)**
Streptococcus pyogenes	1 (33.3%)	2 (66.7%)	0 (0.0%)	0 (0.0%)	3 (100.0%)
MRSA	4 (57.1%)	3 (42.9%)	0 (0.0%)	5 (71.4%)	2 (28.6%)
Enterococcus species	6 (40.0%)	9 (60.0%)	2 (13.3%)	1 (6.7%)	12 (80.0%)
Listeria	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
Gram-negative bacteria					
E. coli	***32 (72.7%)***	***12 (27.3%)***	***3 (6.8%)***	***26 (59.1%)***	***15 (34.1%)***
Klebsiella spp.	***37 (84.1%)***	***7 (15.9%)***	***5 (11.4%)***	***30 (68.2%)***	***9 (20.4%)***
Acinetobacter	***18 (78.3%)***	***5 (21.7%)***	***3 (13.0%)***	***15 (65.2%)***	***5 (21.7%)***
Enterobacter species	12 (92.3%)	1 (7.7%)	2 (15.4%)	9 (69.2%)	2 (15.4%)
Pseudomonas species	3 (50.0%)	3 (50.0%)	0 (0.0%)	5 (83.3%)	1 (16.7%)
Haemophilus influenza	5 (100.0%)	0 (0.0%)	0 (0.0%)	5 (100.0%)	0 (0.0%)
Serratia	2 (66.7%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
Yersinia enterocolitica	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Proteus	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Morganella	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)
Stenotrophomons maltophila	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
Unknown bacteria	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)
Candida albicans	1 (100.0%)	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)

CoNS Coagulase negative staphylococci, *ELBW* extremely low birth weight, *LBW* low birth weight, *NBW* normal birth weight, *MRSA* Methicillin-resistant Staphylococcus aureus, *GBS* Group B streptococcus, *S. Aureus* Staphylococcus Aureus

Table 5 Antibiotic susceptibility of Gram-positive pathogens

Antibiotics	Sensitive N (%)	Resistant N (%)
Ampicillin, *N* = 61	42 (68.8%)	19 (31.1%)
Cefotaxime, *N* = 52	37 (71.2%)	15 (28.8%)
Vancomycin, *N* = 144	141 (97.9%)	3 (2.1%)
Gentamycin, *N* = 53	33 (62.3%)	20 (37.7%)
Ciprofloxacin, *N* = 49	21 (42.9%)	28 (57.1%)
Meropenem, *N* = 37	33 (89.2%)	4 (10.8%)
Amoxicillin-Clavulanate, *N* = 50	39 (78.0%)	11 (22.0%)
Ceftazidim, *N* = 20	15 (75.0%)	5 (25.0%)
Amikacin, *N* = 23	19 (82.6%)	4 (17.4%)
Piperacillin-Tazobactam, **N = 17**	14 (82.4%)	3 (17.6%)

Table 6 Antibiotic susceptibility of Gram-negative organisms

Antibiotics	Sensitive N (%)	Resistant N (%)
Ampicillin, *N* = 39	5 (12.8%)	34 (87.2%)
Cefotaxime, *N* = 98	36 (36.7%)	62 (63.3%)
Gentamycin, *N* = 109	49 (45.0%)	60 (55.0%)
Ciprofloxacin, *N* = 60	34 (56.7%)	26 (43.3%)
Meropenem, *N* = 133	109 (82.0%)	24 (18.0%)
Amoxicillin-Clavulanate, *N* = 83	15 (18.1%)	68 (81.9%)
Ceftazidim, *N* = 90	43 (47.8%)	47 (52.2%)
Amikacin, *N* = 119	79 (66.4%)	40 (33.6%)
Piperacillin-Tazobactam, **N = 99**	70 (70.7%)	29 (29.3%)

preponderance of Gram-negative isolates of which Klebsiella spp. was the most prevalent. The findings in this study showed preponderance both of Gram-positive and Gram-negative (50.0% vs 49.4%) pathogens, which is in contrast with other studies in which usually either Gram-positive or Gram-negative are dominant [37]. Other major isolates found in different studies included *CoNS* [38] staphylococci [39] and *Acinetobacter* [32]. In this study, other dominant pathogens include *α hemolytic streptococcus (11.6%), CoNS (11.3%), GBS (8.6%) and S. Aureus (6.9%).* It has been recognized that the reason for the variation in results could be due to the difference in adherence to infection prevention and control measures.

This study illustrated a high infection of uncommon *α hemolytic streptococcus EOS* among Gram-positive

pathogens, which accounted for 11.6% of all cases, a rate higher than that in the United states and Europe (1% to 5.5%) [40], however similar to the rate in developing countries (11.5%) [41]. Evidence suggests that although the incidence of vaginal colonization in pregnant women is low, *α hemolytic streptococcus* is acquired through a colonized maternal vagina or haematogenously via the placenta. Possible ways of colonization by pneumococci are through oro-genital sexual practices, use of contaminated instruments such as specula and the use of contaminated gloves [42]. However, literature states *α hemolytic streptococcus* should no longer be considered a contaminant if isolated from the blood of a neonate suspected of having sepsis [43].

The findings presented in this study show Gram-negative pathogens were resistant to most of the commonly used antibiotics such as ampicillin (87.2%), gentamycin (55.0%) and cefotaxime (63.3%), similar to the findings of other studies [36, 44]. Additionally, high sensitivity to meroponem and Piperacillin-Tazobactam was seen among Gram-negative pathogens [44]. The Gram-positive bacteria isolated in our study showed the highest sensitivity to Vancomycin, Meropenem and Amikacin, consistent with other findings [35, 45]. On the other hand, they were showed the highest resistance to and ciprofloxacin, similar to other studies [33, 34].

The findings of this study on EOS in Palestine align with and expand upon existing research from the same geographical region, such as the study by Dabaja-Younis et al. [46]. Both studies highlight a significant burden of EOS in Arab populations, though this study reports a higher incidence rate (3 per 1000 live births) compared to other studies from the Gulf region. Notably, Dabaja-Younis et al. report a fivefold higher mortality rate among Arab infants with neonatal sepsis, though antibiotic resistance remains low in their cohort, a contrast to this study's findings [46]. In this study, a high resistance to commonly used antibiotics like ampicillin (87.2%) and gentamicin (55.0%) was observed, particularly among Gram-negative pathogens. However, both studies report high sensitivity to meropenem and piperacillin-tazobactam, suggesting these agents remain critical for treatment in this region. Differences in resistance patterns between this study and findings from Dabaja-Younis et al. may reflect varying hospital practices, local microbial environments, and antibiotic stewardship measures as well as antibiotic usage patterns across the region, warranting further comparative studies. Additionally, variations in study design and sample size could also explain the discrepancies in resistance rates despite geographic proximity.

Our study also determined *CoNS* as one of the major Gram-positive pathogens for EOS, which was consistent with previous studies in Egypt, Asia, and other developing countries [47–49]. Previously, literature has widely described *CoNS* as commensal bacteria of the human skin, and is considered a contaminant of hemo-culture samples when present in a single sample, or with late growth, thus making true bacteremia caused by *CoNS* difficult to distinguish from blood culture contaminants [50]. *CoNS* infection is a major risk factor for premature infants; however, *CoNS* are normal flora of the human skin and mucosa whose pathogenicity has long been ignored and few systematic studies describe their epidemiology in human infections. Nevertheless, colonized *CoNS* pathogens have been reported to be responsible for human infections, particularly in immunocompromised hosts, including neonates [51]. In this study, numerous cases of *CoNS* EOS were excluded due to contamination.

In this study, the distribution of causative organisms for neonatal sepsis differed significantly between preterm and term infants, as well as across birth weight categories. Preterm and LBW neonates showed a higher prevalence of Gram-negative organisms such as *E. coli* and *Klebsiella* spp., consistent with findings in other studies highlighting the vulnerability of these groups to Gram-negative pathogens [52]. In contrast, term and NBW neonates were more affected by Gram-positive organisms, particularly *GBS*, which was more prevalent in term (68%) and NBW (80%) infants. Similar findings have been observed in studies where Gram-positive organisms like GBS and *Staphylococcus aureus* were more common in term and higher birth weight neonates [53]. This pattern highlights the distinct microbiological landscape of neonatal sepsis based on gestational age and birth weight, with preterm and LBW infants being particularly susceptible to Gram-negative infections.

GBS has historically been the most predominant organism causing EOS [11]. Early-onset *GBS* infection rates in the United States reported through the Centers for Disease Control and Prevention's Active Bacterial Core Surveillance Report have declined from 0.6 per 1000 live births in 2000 to 0.25 per 1000 live births in 2018 [4], which is similar to the incidence of *GBS* in this study, which accounted for 0.26 per 1000 live births, and is also similar to findings of other studies conducted in the USA [30, 54]. It has been widely recognized, the use of IAP are the cornerstones of prevention measures that have led to this decline [55–57]. In this study, we found a very low rate (10.3%) of women which were tested for *GBS* colonization screening, which is relatively common globally and within the range of other studies worldwide [58, 59].

Furthermore, our study found that *S. aureus* was one of the most common pathogens accounting for 6.9% of all infections. *S. aureus* is an opportunistic pathogen

able to cause a wide variety of infections in humans and newborns easily receive inoculums from the natural environment before or after delivery [60]. The higher rate of *S. aureus* observed in our study may be due to early horizontal transmission of pathogens from the NICU and delivery rooms or vertical transmission of pathogens colonized in the female vaginal tract after unhygienic obstetric practices [61]. Previous reports have suggested an increase in *Methicillin-resistant Staphylococcus aureus (MRSA)* infections in pregnant and postpartum women coinciding with the increased incidence of *MRSA* infections in NICUs. Vertical transmission from mothers to infants at delivery is a likely route of *MRSA* acquisition by the newborn [61].

Over 60.6% of our sample had C-reactive protein (CRP) levels > 6mg/L. CRP is considered to be a good biomarker for screening of neonatal sepsis since its concentration increases within 6 to 8 h of an infectious episode in neonates and peaks at 24 h [62]. In this study, there was only a single measurement of CRP, which is not a useful aid in the diagnosis of neonatal sepsis, because it lacks sensitivity and specificity. Literature suggests there is need of sequential assessment of CRP values which may help support a diagnosis of neonatal sepsis [63].

The majority of culture positive sepsis in this study was among preterm and low birth weight neonates, similar to findings of studies in Nepal [45] and Saudi Arabia [64]. We also found that more male neonates were diagnosed with sepsis than female neonates (60.6% vs 39.1%). This finding was consistent with the results of studies conducted in Nigeria [65] and Saudi Arabia [64]; however, there has been no scientific reasoning behind this phenomenon.

One of the main strengths in this study is the definition of EOS is based on criteria which identifies only positive blood culture or CSF culture, which makes the diagnoses more accurate. Our study has several limitations. It was a descriptive study and therefore it was not possible to further analyze the association of EOS with potential risk factors. Due to the limitation of inclusion and exclusion criteria, the EOS group may include a few hospital-acquired LOS neonate cases. When analyzing hematology parameters, complete blood count (CBC) and CRP were taken when blood cultures were taken, so these values may reflect mothers and could have been taken within the first six hours of life, thus the interpretation of hematological parameters in this study could be difficult and inaccurate.

Conclusion

This study showed the high prevalence of *E. coli* and *Klebsiella spp.* as Gram-negative bacteria and *α hemolytic streptococcus*, *CoNS* and *GBS* as Gram-positive bacteria among neonates with EOS. In Palestine, emergence of antibiotic resistance among bacterial pathogens from neonatal sepsis is a major cause for treatment failure, higher morbidity and mortality. Proper antibiotic guidelines and its effective implementation could be a milestone for revolution in the field of antibiotic resistance control. These findings provide guidelines for the selection of empirical antimicrobial agents in the study sites and suggest that there is need for future studies to assess further the epidemiology of neonatal sepsis, causative risk factors, bacteriological profiles and antibiotic susceptibility patterns of pathogens in Palestinian hospitals to develop national guidelines for management of neonatal sepsis.

Abbreviations

AST	Antimicrobial susceptibility test
CBC	Complete blood count
CLSI	Clinical Laboratory Standard Institute standards
CRP	C-reactive protein
CoNS	Coagulase negative staphylococci
CS	Caesarean section
CSF	Cerebrospinal fluid
DIC	Disseminated intravascular coagulation
E.coli	Escherichia coli
ELBW	Extremely low birth weight
EONS	Early-onset neonatal sepsis
EOS	Early-onset sepsis
GA	Gestational age
GBS	Group B Streptococcus
IAP	Intrapartum antibiotic prophylaxis
IVD	Induced vaginal delivery
LBW	Low birth weight
LOS	Late-onset sepsis
LP	Lumbar puncture
MRSA	Methicillin-resistant Staphylococcus aureus
NBW	Normal birth weight
NICU	Neonatal intensive care unit
NVD	Normal vaginal delivery
PBSI	Primary blood stream infection
PICC	Peripherally inserted central catheter
PMC	Palestine Medical Complex
ROM	Rupture of membranes
S. Aureus	Staphylococcus Aureus
UTI	Urinary tract infection
UVC	Umbilical venous catheter
WBC	White blood count
WHO	World Health Organization

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Authors' contributions

RB and HA (H. Allabadi) wrote the original manuscript text. HK and RB contributed to the conceptualization, study design, methodology, and interpretation of the data. HA (H. Allabadi) conducted the formal data analysis and contributed to the interpretation of the data. RB, AB, DS, FH, ND, RN, RS, RB (R. Bakri), RK, SA, and SH (S. Herzallah) conducted the data collection. RB, HA (H. Atout), JI, RE and HK assisted in the project administration and supervision. AM, DA, NA, GZ, HM, MH, SH (S. Hamada) contributed to the validation of the

study. All authors revised the manuscript and approved the final version to be published.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the principles outlined in the Declaration of Helsinki to ensure ethical standards in research involving human participants and/or human data. Ethical approval was obtained from Hospital Administration at the Palestine Ministry of Health and the administration of each hospital included in the study. Permission to access medical records of neonates and their mothers was obtained from the hospital director at each hospital. Informed consent was waived for participants included in the study by the Institutional Review Board of Maqassed Hospital. All other ethical considerations were strictly adhered to throughout the duration of the study, ensuring the preservation of confidentiality and privacy for all participants. Personal and medical information was collected and analyzed anonymously. Codes were used instead of names to ensure confidentiality.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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