

# Bacterial profile and drug resistance patterns in neonates admitted with sepsis to a tertiary teaching hospital in Ethiopia

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## Research article

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## **Abstract**

Background : Tackling neonatal infections and antibiotic resistance remains a challenge in low-income countries where neonatal mortality is high and antibiotic resistance is growing. The aim of this study was to identify bacterial etiologies and their drug resistance patterns in neonates admitted with diagnosis of sepsis to neonatal intensive care unit at Jimma Medical Center in Ethiopia.

Methods : A prospective longitudinal study was conducted from April to October 2018. A total of 313 clinical specimens (211 blood and 102 cerebrospinal fluid) were processed for 238 neonates suspected to have sepsis. Blood culture was done using BD BACTEC FX40 automated system. Bacterial identification and antibiotic susceptibility testing were done according to standard microbiological techniques.

Results : Bacterial etiologies were isolated from 62.1% (131/211) and 3.9% (4/102) of blood and cerebrospinal fluid cultures respectively. The predominant bacteria isolated from blood were Coagulase negative Staphylococcus 27.5% (36/131), followed by *S. aureus* 20.6% (27/131), *Klebsiella* species 14.5% (19/131), and *Acinetobacter* species 10.7% (14/131). Nearly 85% of the isolates were multidrug resistant, predominantly observed in Gram-negative bacteria. Among locally available antibiotics, only meropenem for Gram-negatives and vancomycin for Gram-positives were found to be largely effective.

Conclusion : Bacterial pathogens identified in the study were highly resistant to available antibiotics. Thus, an effort to reduce neonatal mortality in the setting should focus on improving diagnostics for neonatal infection and containment of antimicrobial resistance.

## **Background**

Neonatal infection remains one of the most common causes of morbidity and mortality in newborns with over one million deaths annually; 99% of these deaths occur in resource-limited countries [1, 2]. Neonatal sepsis can be classified based on the time of occurrence as early-onset and late-onset sepsis depending on the age at onset. Early-onset neonatal sepsis (EONS) is defined by its occurrence with seven days of life and is commonly caused by organisms acquired from the mother's genital tract during delivery. The most common causative organisms are Group B Streptococcus, Escherichia coli and *Klebsiella pneumoniae*. Late-onset neonatal sepsis (LONS) occurs after 7 days of life and is usually caused by pathogens acquired during hospitalization or delivery. The most common causative organisms are coagulase-negative Staphylococcus (CoNS), *Staphylococcus aureus*, *Enterococcus* species, and Enterobacteriaceae [1, 3, 4].

It is well documented that neonates with sepsis have an increased risk of developing meningitis, which on its own would deteriorate the prognosis of such neonates [5, 6]. Data from both high- and low-income settings have shown that meningitis affects 0.3 to 3% of neonates with early onset neonatal sepsis [7, 8] and up to 30% of cases with LONS [6, 9–11]. Hence, there should be high index of suspicion for bacterial meningitis whenever neonatal sepsis is diagnosed, especially in cases of LONS [9, 10].

Early diagnosis and treatment of neonatal sepsis are essential to prevent severe and life-threatening complications. However, accurate diagnosis of neonatal infection remains a challenge, particularly in resource-limited settings, due to variable and non-specific clinical features and the difficulty of obtaining infection markers in the early stage [12]. Poor diagnostic facilities and lack of skilled health workforce in such settings add further challenge to achieve the goal of reducing neonatal sepsis globally. In real-life clinical practice, treatment is additionally challenging due to

the absence of susceptibility patterns of bacterial etiologies of sepsis and the lack of accurate diagnostic markers [13, 14]. Antibiotic treatment is also increasingly complicated by limited options and the emergence of high level and more extensive antimicrobial resistance against the existing antibiotics in several developing countries [15].

Tackling neonatal sepsis and antibiotic resistance is extremely challenging in low-income countries where neonatal mortality is high and antibiotic resistance is growing [16]. In these countries, isolation of etiologies of sepsis as well as determining drug susceptibility patterns of the organisms is difficult. As a result, overutilization of antibiotics is inevitable [17, 18]. Consequently, multidrug resistant (MDR) organisms have emerged as important causes of neonatal sepsis in these settings in recent years. These extremely drug resistant pathogens include extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae [19–21], methicillin-resistant *S.aureus* (MRSA) [21, 22], and MDR *Acinetobacter baumannii* [23], among other MDR organisms. Different studies have shown that a high prevalence of sepsis due to MDR bacterial pathogens in intensive care settings dramatically increases mortality of newborns, especially in developing countries [2, 20, 24].

Essential data on the burden of severe bacterial infections in neonates and bacterial causes are scarce in Ethiopia, and the magnitude of antibiotic resistance remains unclear. Thus, a better understanding of the driving forces of bacterial sepsis and transmission is needed to help the fight against neonatal sepsis and antibiotic resistance. Hence, this study aimed to determine the profile and drug resistance patterns of bacteria causing sepsis in neonates admitted to a tertiary teaching hospital in Ethiopia.

## **Materials And Methods**

### **Setting**

Jimma Medical Center (JMC) is a university hospital in southwest Ethiopia with over 700 beds and catchment population of over 20 million. The study was conducted at the neonatal intensive care unit (NICU) of the hospital, which is a second level NICUs with a total bed capacity of 50 and an annual admission of 1800 to 2400 neonates. Neonates with a broad diversity of cases including infectious diseases, metabolic and genetic disorders, congenital malformations and surgical conditions are admitted and treated at the NICU. Neonates admitted to the NICU arrive from delivery units of the hospital itself and from various health facilities in the catchment area.

### **Study design**

A prospective longitudinal study was conducted from April to October 2018. All neonates admitted to NICU with clinical diagnosis of sepsis and investigated with blood and/or CSF culture during the study period were included in the study.

### **Data collection**

A structured case reporting format was used to collect background data and clinical information. One sample of 1-3 milliliters venous blood was collected from the neonates by staff nurses. Additionally, 2-3ml of cerebrospinal fluid (CSF), in the absence of contraindications, was also collected by resident physician from neonates suspected to have sepsis. The specimens were collected following the principles of aseptic specimen collection and were immediately transported to the microbiology laboratory of JMC for processing and analysis.

### **Isolation and identification of pathogens**

The blood specimens were inoculated into a BD BACTEC Peds Plus/F bottle. The bottles were then incubated in the BD BACTEC™ FX40 automated culture machine for a maximum of five days until they were flagged as “negative” or “positive” for growth. Positive bottles were taken out from the machine and sub-cultured on Blood, Chocolate, and MacConkey agar (Oxoid, England). The CSF specimens, on the other hand, were directly inoculated on Blood, Chocolate and MacConkey agar (Oxoid, England) plates within 30 minutes of collection.

The chocolate and Blood agar plates from both blood and CSF specimens were incubated in a candle jar to create a condition of 5–10% CO<sub>2</sub>. All the plates were incubated at 35–37°C aerobically for 18–24 hours. After overnight incubation, all the inoculated plates were inspected and organisms grown on the plates were identified according to the standard microbiological identification techniques [25].

## Antimicrobial susceptibility testing

Antibiotic susceptibility testing was carried out using Kirby-Bauer disc diffusion technique on Mueller-Hinton agar (Oxoid, England) according to Clinical Laboratory Standard Institute guidelines. Penicillin (1µg), oxacillin (1µg), cefoxitin (30µg), ampicillin (10mg), erythromycin (15mg), clindamycin (2mg), trimethoprim-sulphamethoxazole (1.25µg), amoxicillin/clavulanic acid (10mg), ceftazidime (30µg), cefepime (30µg), ceftriaxone (30µg), gentamicin (10mg), ciprofloxacin (5mg), tetracycline (30mg), chloramphenicol (30mg), ampicillin-sulbactam (10mg), vancomycin (30µg), and meropenem (10mg) were used. All the antibiotic discs used for the study were obtained from Oxoid Ltd., Basingstoke, Hampshire, UK. Reference strains of *E. coli* ATCC 25922 and *S. aureus* ATCC 25923 were used to control the reliability of antimicrobial susceptibility tests.

## Statistical analysis

The data were entered using Epi Data version 3.1 and exported to SPSS version 25 and Microsoft excel for analysis. Descriptive statistics were used to show the frequency of bacterial agents and their drug resistance pattern.

## Ethical considerations

Ethical approval was obtained from both Jimma University Institute of Health Institutional Review Board, Ethiopia (protocol number: IHRPGD/274/2018) and the Ethics Committee at the Medical Faculty of Ludwig Maximilian University of Munich, Germany. Written informed consent was obtained from the families or guardians of each neonate before they were recruited into the study. All the information collected were kept confidential and recorded in an anonymized fashion. All the microbiologic results of each neonate were immediately reported to the treating physician so that s/he could modify the treatment of the patient accordingly.

## Results

Culture and antimicrobial susceptibility testing was performed for 313 clinical specimens (211 blood and 102 CSF) from 238 neonates suspected to have sepsis. Of these, 75 neonates had both blood and CSF cultures done. Overall, 63.5% (134/211) of the blood cultures and 3.9% (4/102) of the CSF cultures were found to be positive for microbial growth. From these clinical specimens (blood and CSF), a total of 135 bacterial and 8 fungal etiologies were isolated. Sepsis episodes caused by Gram-positive bacteria, Gram-negative bacteria, and *Candida* species were 50.3% (70/139), 43.9% (61/139), and 5.8% (8/139), respectively. Among the 131 bacterial pathogens isolated from blood culture, the predominant isolates were CoNS 27.5% (36/131), *S. aureus* 20.6% (27/131), *Klebsiella* spp.

14.5% (19/131), and *Acinetobacter* species 10.7% (14/131) (Figure 1). Of these, double bacterial isolates were detected in cultures from five neonates.

From CSF samples, two *Acinetobacter* spp. and two *K. pneumoniae* were isolated. In one neonate, three types of bacterial pathogens were isolated simultaneously; *S. aureus* and *Acinetobacter* species from blood culture and *K. pneumoniae* from CSF.

CoNS – coagulase-negative *Staphylococcus*, GBS – group b *Streptococcus*, spp – species

**Figure 1:** Etiologies identified from blood culture in neonates admitted with sepsis to neonatal intensive care unit of Jimma Medical Center, Ethiopia

#### **Antibiotic susceptibility pattern of isolates**

The most common Gram-negative bacterial pathogens isolated in this study (from both blood and CSF) were *Klebsiella* spp., *Acinetobacter* spp., and *Citrobacter* spp. accounting for 32.3% (21/65), 24.6% (16/65), and 15.4% (10/65) of the isolates, respectively. All of the isolated *Klebsiella* spp. were resistant to ampicillin, amoxicillin/clavulanic-acid, cefoxitin, ceftriaxone, cefepime, chloramphenicol, sulfamethoxazole-trimethoprim, and tetracycline. Similarly, all isolates of *Acinetobacter* spp. were found to be resistant to ampicillin, amoxicillin/clavulanic acid, cefoxitin, ceftazidime, ceftriaxone, chloramphenicol, tetracycline and sulfamethoxazole-trimethoprim. However, all isolates of *Klebsiella* spp. were susceptible to meropenem, whereas 25% of *Acinetobacter* spp. were meropenem resistant. The other commonly isolated Gram-negative bacteria causing neonatal sepsis, *Citrobacter* spp., also showed MDR patterns, being resistant to ampicillin, amoxicillin/clavulanic acid, cefoxitin, ceftazidime, ceftriaxone, cefepime, and tetracycline. Three (30%) of the isolated *Citrobacter* spp. were resistant to meropenem (Table 1).

**Table 1:** Antibiotic resistance patterns of Gram-negative bacterial pathogens in neonates admitted with sepsis to neonatal intensive care unit of Jimma Medical Center, Ethiopia

Antibiotics	<i>Klebsiella</i> spp. (n=21)	<i>Acinetobacter</i> spp. (n=16)	<i>Citrobacter</i> spp. (n=10)	<i>E.</i> <i>coli</i> (n=5)	<i>P.</i> <i>aeruginosa</i> (n=5)	*Other GNB (n=8)	Total (n=65)
Ampicillin	100%	100%	100%	100%	100%	100%	100%
Amoxicillin/clavulanate	100%	100%	100%	100%	100%	100%	100%
Cefoxitin	100%	100%	100%	60%	100%	100%	100%
Ceftazidime	95%	100%	100%	60%	100%	100%	95%
Ceftriaxone	100%	100%	100%	40%	100%	100%	95%
Cefepime	100%	81%	100%	40%	100%	100%	91%
Tetracycline	100%	100%	100%	80%	100%	100%	98%
Chloramphenicol	100%	100%	90%	20%	0%	88%	74%
Trimethoprim-sulphamethoxazole	100%	100%	90%	60%	80%	88%	92%
Ciprofloxacin	76%	31%	30%	20%	20%	63%	48%
Gentamycin	76%	50%	80%	40%	20%	63%	62%
Meropenem	0%	25%	30%	0%	60%	12.5%	17%

\* Includes: *Enterobacter* spp. (3), *Providencia* spp. (3), *Serratia* spp. (1), and *Proteus mirabilis* (1)

GNB – Gram-negative bacteria

Coagulase negative *Staphylococci* (51.4%; 36/70) and *S. aureus* (38.6%; 27/70) were the most common Gram-positive bacteria isolated from the study participants. The CoNS group showed high level of resistance to penicillin (89.0%) and oxacillin (83.3%). Similarly, *S. aureus*, showed a high rate of resistance against sulfamethoxazole-trimethoprim (88.9%), penicillin (85.2%), tetracycline (74.1%) and erythromycin (70.4%). Moreover, 63.0% of *S. aureus* were methicillin resistant (MRSA). On the other hand, the *Micrococcus* spp. identified in three neonates were found to be susceptible to almost all antibiotics tested (Table 2).

**Table 2:** Antibiotic resistance pattern of isolated Gram-positive bacterial pathogens in neonates admitted with sepsis to neonatal intensive care unit of Jimma Medical Center, Ethiopia

Antibiotics	CoNS (n=36)	<i>S. aureus</i> (n=27)	*Other GPB (n=7)	Total (n=70)
Penicillin	89%	85%	71.4%	86%
Oxacillin	83%	63%	71.4%	74%
Cefoxitin	83%	63%	71.4%	74%
Erythromycin	56%	70%	57.1%	61%
Clindamycin	33%	33%	57.1%	36%
Ceftriaxone	78%	67%	57.1%	73%
Tetracycline	81%	74%	71.4%	76%
Trimethoprim-sulphamethoxazole	89%	89%	57.1%	86%
Vancomycin	6%	11%	0%	7%

\* Includes: Group B *Streptococcus* (n=3), *Micrococcus* spp. (n=3), and *L. monocytogenes* (n=1)

GPB – Gram-positive bacteria

Resistance to more than one agent in three or more antimicrobial categories was seen in 84.4% (114/135) of the bacterial isolates. MDR patterns were observed predominantly in Gram-negative bacterial pathogens. All of the isolated *Klebsiella* spp., *Acinetobacter* spp., *P. aeruginosa*, *Providencia* spp., *Serratia* spp., *P. mirabilis*, and 90% of *Citrobacter* spp. were MDR (Figure 2). Amongst the isolated Gram-negative MDR strains, one strain of each of *Providencia* spp., *Klebsiella* spp. and *Citrobacter* spp., and two strains of *Acinetobacter* spp. were resistant to all of the tested antibiotics, including carbapenem antibiotics.

MDR – multidrug resistant, NMDR – non-multidrug resistant, GNB – Gram-negative bacteria, GPB – Gram-positive bacteria.

**Figure 2:** Distribution of MDR and non-MDR patterns of bacterial isolates in neonates admitted with sepsis to neonatal intensive care unit of Jimma Medical Center, Ethiopia

Twenty-four, 10.1% (24/238) of the neonates died in the hospital. Of these, 66.7% (16/24) had positive blood and/or CSF culture and a total of 17 pathogens were identified from them. The predominant isolates in these groups were *Klebsiella* spp. (n=5), *Acinetobacter* spp. (n=2), *P. aeruginosa* (n=2) and *Citrobacter* species (n=2), all of which were MDR. *E. coli* and *Enterobacter* spp. isolated in this group were also found to be MDR. Though the sample size of this group is too small to determine any statistical association, it is highly possible that MDR organisms might have contributed to neonatal mortality at the hospital. It is also important to note here that 81% (13/16) of the deaths in culture-confirmed cases occurred in patients identified with Gram-negative bacterial sepsis.

## Discussion

In this study, blood culture was able to identify etiologic agents in 63.5% of neonates suspected to have sepsis. This proportion is higher than that in findings from recent similar studies in different parts of Ethiopia; 46.6% in Gondar [26], 44.7% in Addis Ababa [27], and 29.4% in Asella [28]. Our finding is also higher than in similar studies

from other low- and middle-income countries; 49.7% in Tanzania [14], 43.4% in India [29], 16.9% in Nepal [30], and 12.2% in Iran [31].

The high rate of culture positivity in our study may be explained by various reasons. First of all, the participants were neonates admitted to NICU only, excluding neonates in relatively stable medical conditions admitted to regular pediatric ward. Secondly, we used a highly sensitive automated blood culture system (BD BACTEC™ Blood Culture) [32] unlike in most of the other studies mentioned above where manual systems were used. Thirdly, the fact that we used only one blood specimen for culture, contamination might have also contributed to increased culture positivity. Nevertheless, in such low-income setting where studies on neonatal infections are limited, such a finding may also be reflecting a reality on the ground, since sample taking was part of routine clinical procedures and not investigator initiated. However, involved staffs do undergo regular trainings on appropriate and sterile sample-taking techniques.

Group B Streptococcus, E. coli and K. pneumoniae in EONS and CoNS, S. aureus, and Enterococcus spp. in LONS are major cause of neonatal sepsis [1, 3]. In our study however, the common etiologies identified were CoNS, S. aureus, Acinetobacter spp., Klebsiella spp. and Citrobacter spp. These bacteria are mostly acquired from the hospital environments, health professionals, and medical devices [33, 34]. Moreover, as majority of our study participants (84.1%) had early onset neonatal sepsis, the bacterial etiologies identified in our study somehow deviate from expectations [1, 3, 4]. One of the possible explanations is that about 68% of the neonates were delivered at the same hospital where high rate of hospital acquired infection by these organisms has been documented [35–37]. On the other hand, recent similar studies in Ethiopia have revealed that CoNS, S. aureus and Klebsiella spp. are major cause of neonatal sepsis in the country [26–28]. These evidences suggest that in settings where infection prevention and control practices are not properly implemented [38, 39]; infections by these agents constitute a significant threat to neonates and other vulnerable populations.

Concerning to drug resistance, the isolates in the present study were resistant against commonly used antibiotics in the area and high frequency of MDR bacterial pathogens were observed predominantly among the Gram-negative bacteria. Recent studies in Ethiopia, India, Nepal, and China also showed high levels of resistance in Gram-negative organisms against ampicillin (85%, 78%, 100%, 80%), respectively, and ceftriaxone (57%, 100%, 100%, 50%), respectively [26, 29, 30, 40]. Low level of resistance was observed against meropenem (17%) in Gram-negative bacteria and vancomycin (7%) in Gram-positive bacteria. A potential explanation is that these two antibiotics are expensive and not widely available in the setting studied and hence less frequently prescribed. Among the older antibiotics, only ciprofloxacin (48% resistance) and clindamycin (35% resistance) showed better in vitro efficacy against Gram-negative and Gram-positive bacteria respectively.

The MDR patterns in both Gram-negative and Gram-positive bacteria in our study (84.4%) is by far higher than national and global reports: Ethiopia (65%) [26], Jordan (69%) [23], and China (50%) [40]. Moreover, the high rates of MRSA and Acinetobacter spp. resistant to almost all antibiotics available in the setting are serious concerns for the healthcare system in the region and beyond. Unavailability of microbiologic diagnostic facilities, poor infection prevention and control practices, lack of antimicrobial quality control, lack of control on antimicrobial utilization and absence of proper antimicrobial resistance surveillance system in the country and at the hospital in particular might have contributed to this alarming rate of MDR pattern.

The proportion of culture confirmed meningitis in neonates with sepsis is only 4%. As most of the neonates had EONS, the finding is concordant with existing global evidences [7, 8]. However, this finding cannot be generalized to

all neonates admitted to the hospital and other settings in Ethiopia as our study has excluded neonates admitted to regular pediatric wards.

Our study is one of few studies on etiologies and AMR patterns in neonatal sepsis in Ethiopia. We believe that the findings in this study complement what has already been done and could provide important data for policy-level intervention to tackle neonatal mortality and antimicrobial resistance. However, the fact that our study is limited to one facility, a tertiary teaching hospital, and that only neonates admitted to NICU were included may limit the generalizability of the findings. Moreover, only one blood sample was taken from the neonates for culture, contamination during specimen collection might have contributed to the high rate of culture positivity in our study.

## Conclusions

This study has shown that MDR CoNS, *S. aureus*, and Gram-negative bacilli (*Klebsiella*, *Acinetobacter*, and *Citrobacter* spp.) were the leading causes of neonatal sepsis at the hospital. The emergence of MDR pathogens in the country, including resistance to reserve antimicrobials and the unmet target in reduction of neonatal mortality, deserve intervention at policy-level. This should be done through development of locally acceptable and applicable guidelines, adhering to standard evidenced based practices, commitment to rational use of antimicrobials, improving diagnostic facilities and implementing, nationwide AMR surveillance system. Future research should also be carried out focusing on identification of appropriate local empiric therapies with improved susceptibility profiles for timely and effective treatment.

## Abbreviations

AMR	
antimicrobial resistance	
ATCC	
American Type Culture Collection	
CoNS	
Coagulase negative Staphylococcus	
CSF	
Cerebrospinal fluid	
EONS	
Early onset neonatal sepsis	
ESBL	
Extended spectrum beta lactamase	
JMC	
Jimma Medical Center	
LONS	
Late onset neonatal sepsis	
MDR	
Multidrug resistance	
MRSA	
Methicillin resistance <i>Staphylococcus aureus</i>	
NICU	
Neonatal intensive care unit	

Spp  
Species  
SPSS  
Statistical Package for social science

## Declarations

### Ethics approval and consent to participate

This study was approved by the Institutional Review Board (IRB) of Jimma University Institute of Health ethical committee, Ethiopia and The Ethics Committee at the Medical Faculty of LMU Munich, Germany. Written informed consent was also obtained from parents and/or guardians of the neonate.

### Consent for publication

Not applicable.

### Availability of data and materials

The dataset will be available from the corresponding author on reasonable request.

### Competing interests

All the authors declare that they have no competing interests regarding this work.

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### Authors' contributions

EKG, SA, MB, MG, GKB, AW and GF conceptualized and designed the study protocol. BE, MG, MB, EKG, SA, NW and GT coordinated and supervised data collection. MG and EKG drafted the manuscript and all the authors critically reviewed and approved the final manuscript in its current form and agreed to be accountable for all aspects of the work.

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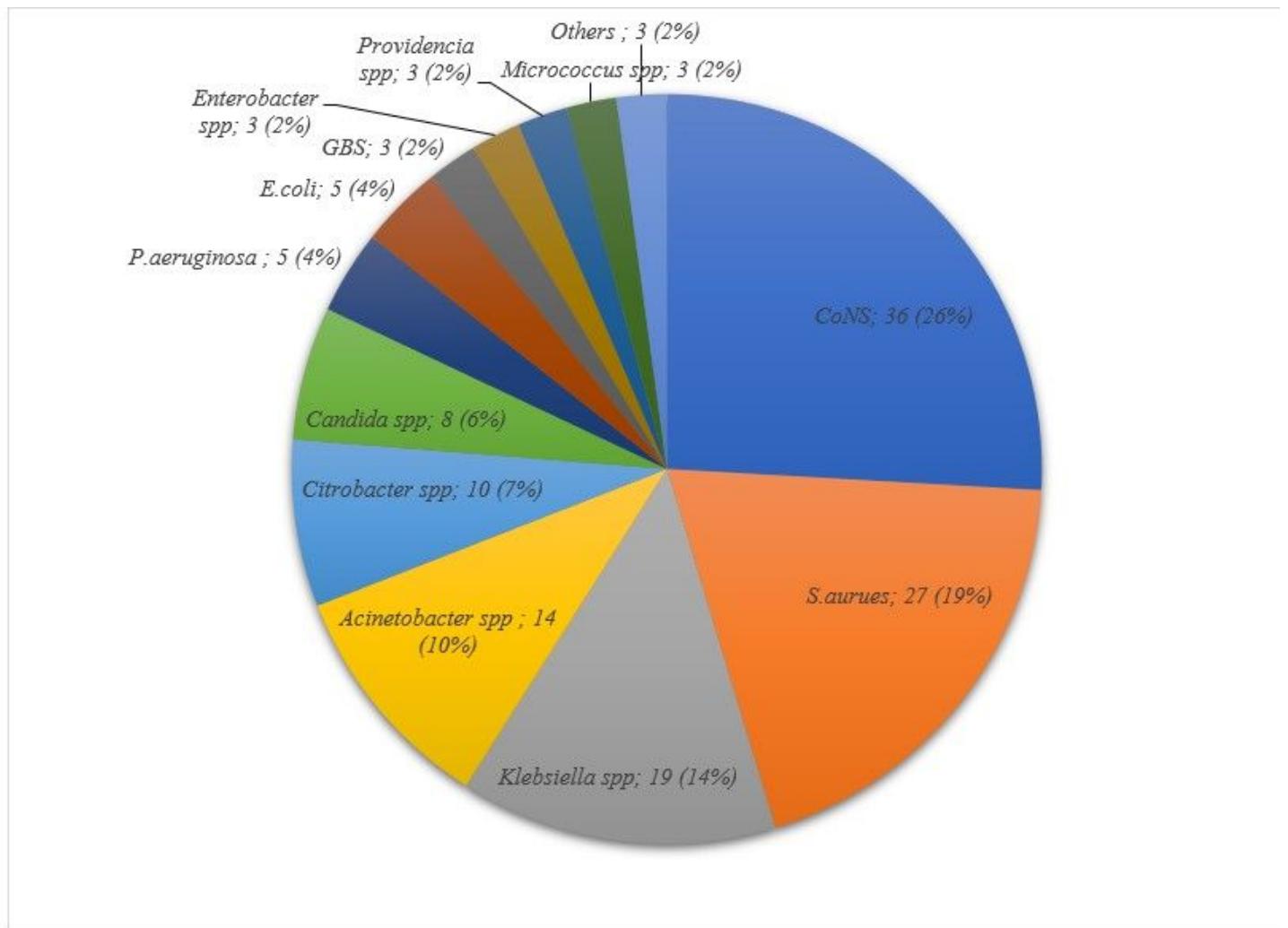
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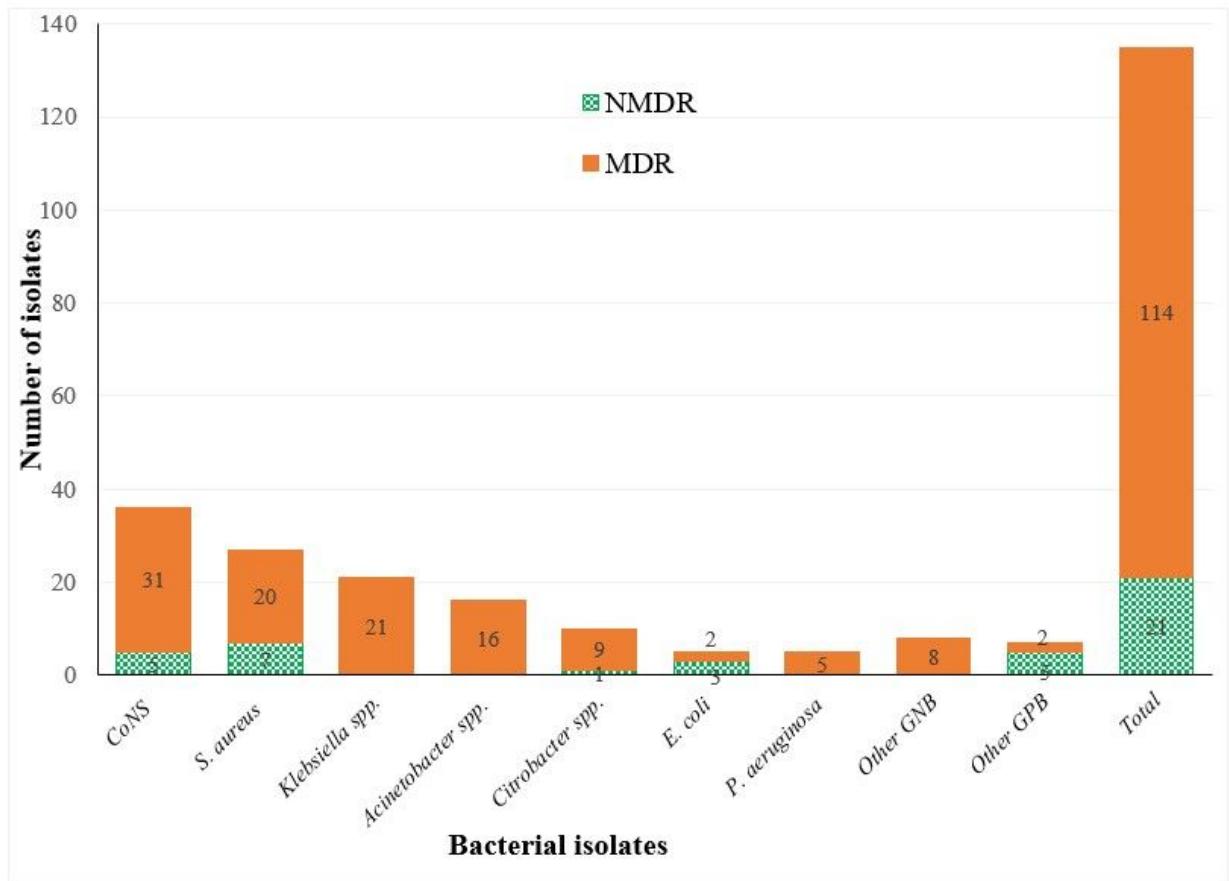
## Figures



CoNS – coagulase-negative *Staphylococcus*, GBS – group b *Streptococcus*, spp – species

**Figure 1**

Etiologies identified from blood culture in neonates admitted with sepsis to neonatal intensive care unit of Jimma Medical Center, Ethiopia



MDR – multidrug resistant, NMDR – non-multidrug resistant, GNB – Gram-negative bacteria, GPB – Gram-positive bacteria.

**Figure 2**

Distribution of MDR and non-MDR patterns of bacterial isolates in neonates admitted with sepsis to neonatal intensive care unit of Jimma Medical Center, Ethiopia