Clinical Manifestation of Neonatal Sepsis and Prevalence of ESBL-Producing Bacteria in South Asia

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A thesis submitted to the Department of Mathematics and Natural Science in partial fulfillment of the requirements for the degree of B.Sc. in Microbiology

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Declaration

It is hereby declared that Clinical Manifestation of Neonatal Sepsis and Prevalence of ESBL-Producing Bacteria in South Asia

1. The thesis submitted is my/our own original work while completing degree at Brac University.

2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.

3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.

4. We have acknowledged all main sources of help.

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Abstract

A fatal infection called neonatal sepsis can strike infants as early as 28 days after birth. It contributes remarkably to newborn morbidity and mortality, especially in developing countries. Neonatal sepsis has a complicated pathophysiology that is influenced by several variables, including the immune system of the host, the pathogenic organism, and any underlying medical problems. The most common causative agents of neonatal sepsis are bacteria, such as *Group B Streptococcus* (GBS), *Escherichia coli* (*E. coli*), and *Klebsiella pneumoniae*. Neonatal sepsis, though, can also be brought on by viruses and fungi. Depending on the newborn's age, the etiologic agent, and the intensity of the infection, the clinical signs and symptoms of neonatal sepsis can change. There are two types of sepsis: early-onset (EOS), which strikes during the first 72 hours of life, and late-onset (LOS), which strikes after that time. The accurate diagnosis of neonatal sepsis depends on the newborn's clinical appearance and the outcomes of laboratory investigations, like blood cultures. The causative organism and the seriousness of the infection determine the newborn sepsis treatment. Antibiotics are usually required. The entire neonatal sepsis treatment process is difficult, particularly in developing nations. Antibiotic resistance, a lack of resources, a lack of awareness, etc. are a few of the difficulties. Despite the difficulties, there is a growing amount of research on successful newborn sepsis prevention methods and treatment approaches. We can contribute to a reduction in the number of infants who acquire and succumb to this dangerous infection by putting these precautions and tactics into practice.

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CHAPTER-1

Introduction

Especially in the context of a developing nation, where it frequently appears as one of the leading causes of newborn morbidity and mortality, a serious public health concern is neonatal sepsis. The clinical state of life-threatening organ malfunction known as sepsis is brought on by an unbalanced immune response to infection (Neonatal Sepsis - Pediatrics, n.d.). Neonatal sepsis, a systemic infection that develops within the first 28 days of life, includes pneumonia, meningitis, and bloodstream infection. Through common research, the clinical factors those are identified as significant factors of risk for sepsis in development of neonates are usually, rupture of premature of membrane (PROM), low birth weight that is less than 37 weeks and prematurity, foul smelling liquor that extracted through vaginal path and meconium-stained amniotic fluid (MSAF). In some cases the blood culture might be positive with bacteria like *E.coli, Klebsiella pneumoniae, Group B Streptococcus, Staphylococcus aureus* and *Salmonella typhi* in some cases. Nearly all risk factors were present in both cases of positive and negative culture (Risk Factors in Early Neonatal Sepsis, 2006). There could be multiple signs are as well as Non-specific, with fewer spontaneous activities, bradycardia, temperature instability (hypothermia or hyperthermia), intestinal distention, vomiting, diarrhoea, and other symptoms of respiratory distress. The clinical diagnosis is made based on the findings of a blood, CSF, or urine culture. Antibiotic drugs ampicillin, either gentamicin or cefotaxime are used as the first line of treatment before being quickly narrowed down to medications for particular organism. But either antibiotic resistance or ESBL producing bacteria are causing hindrance treatment procedures nowadays (Nyma et al., 2020).

Approximately 1.6 million newborns globally die each year from neonatal sepsis, with low to middle income or developing nations accounting for 99% of these deaths. In 14 countries, the majority of which were low- to middle-income nations, a meta-analysis found that between January 1979 and May 2019 there were 2 797 879 live births and

29 608 instances of sepsis. Neonatal sepsis incidence was 2824 instances per 100 000 live births overall, according to a random-effects estimator, with an estimated mortality rate of 17.6%. (Fleischmann et al., 2021).

Another estimation showed, Only in South Asia did sepsis-related newborn deaths account for 38.9% of all neonatal fatalities in 2013.The highest rates of newborn sepsis are seen in South Asia and sub-Saharan Africa, with South Asia accounting for 38.9% of all sepsis-related neonatal deaths globally in 2013. The prevalence of culture-positive sepsis is 15.8 per 1000 live births, with a median case fatality rate of 34.4% for neonates who had the condition similar to other types of sepsis, early onset sepsis is far more common than late onset sepsis (Chaurasia et al., 2019).

Neonatal sepsis may be classified into one of two categories: Early-onset sepsis (EOS), which is defined as the appearance of sepsis symptoms within 72 hours of life while Late-onset sepsis (LOS) is defined as onset of features of sepsis diagnosed after 72 hours of life. The fact that differentiates between EOS and LOS is the time of prognosis and diagnosis of the sepsis in a neonate.

In most cases, bacteria collected during delivery induce early-onset newborn sepsis. Within six hours of delivery, most newborns are vulnerable to symptoms (Neonatal Sepsis - Pediatrics, n.d). Early-onset sepsis (EOS) continues to be a major cause of morbidity and mortality in newborns. Although many EOS cases are largely apparent in term infants, preterm infants have a higher infection-associated death rate, which is inversely proportional to gestational age. According to a 23-year study, EOS is more common than LOS in preterm newborns with gestational ages under 37 weeks. In different nations and their various regions, the frequency of EOS has reduced over the past several decades. It is noteworthy that the implementation of efficient intrapartum antibiotic prophylaxis made this feasible. When analysing the blood cultures from neonates that are between term (GA>37 weeks) and moderately preterm newborns (GA 28-36 weeks) found with EOS, *Group B streptococci* (GBS) are the most frequently recognized pathogens.

On the other hand, *Escherichia coli* is typically the most frequently discovered pathogen in blood cultures in extremely preterm newborns (GA 28 weeks). Other bacterial infections that cause EOS have been found to have less well-described patterns. Despite such precautions, there is currently growing concern about microorganisms that cause EOS becoming less and less resistant to antibiotics, particularly Gram-negative pathogens where there are typically few effective therapeutic alternatives (Vatne et al., 2021). Occasionally, asymptomatic gonorrhea develops during pregnancy. so *Neisseria gonorrhoeae* may rarely be a pathogen causing EOS (Neonatal Sepsis - Pediatrics, n.d.).

Late-onset neonatal sepsis (LOS) is most frequently obtained from the environment or the caregiver the neonate is exposed with. Usage of intravascular devices particularly the usage of central vascular catheters is a crucial reason accounted for with *Staphylococci*. Likewise, Infants EOS with low birth weight are more likely to experience LOS where *E. coli* is also becoming an increasingly recognized pathogen. Contaminated feeding could be identified reason as isolation of *Enterobacter cloacae* from blood or cerebrospinal fluid (CSF) while cultured in LOS. Also, contaminated respiratory equipment with *Pseudomonas aeruginosa* is suspected in occurrences of sepsis or pneumonia that originated in hospitals (Neonatal Sepsis - Pediatrics, n.d.).

ESBL goes for extended spectrum beta-lactamase which is an enzyme generated by certain bacteria strains. Because the enzymes of bacteria hydrolyse most penicillin and cephalosporins, including oxyimino- β-lactam compounds. Antibiotics are often failed to resist ESBL-producing bacteria because they are capable of producing beta lactamase enzyme to inhibit the beta lactam ring in beta lactam antibiotics like, penicillin and some cephalosporins, carbapenems etc. that doctors use to treat infections. Though, a combination of clavulanic acid, tazobactam and sulbactam like compounds are often combined with antibiotics to make them beta lactamase resistant. But as the time passes through microorganisms those were resistant to such drugs are rapidly being resistant towards beta lactamase resistant drugs, which is because of the extended spectrum of beta lactamase, a growing concern to treat neonates with sepsis.

Random antibiotics use ultimately contributes to spread of gram-negative bacterial sepsis in neonatal units over time due to an improved chance of survival for preterm infants and imprudent neonates. The advent of resistant infections, such as gram-negative bacteria that produce extended-spectrum b lactamases (ESBLs), is a complicating concern (Sehgal et al., 2007). Ultimately a potential threat for curing the neonatal sepsis due to unavailability of most broad-spectrum antibiotics. Commonly reported gram-negative bacteria (GNB) in ESBL prevalence are *Klebsiella* isolates, *Enterobacter,* and *Escherichia coli* strains also, coagulase negative *Staphylococci* and group B *streptococc*i and *Pseudomonas aeruginosa* are being found rarely. The fact, what makes ESBLs so vicious is that they are plasmid-associated, and plasmids can exchange with various bacterial species. These plasmids may also contain genes that cause resistance to more advantageous antibiotics, such as sulfamethoxazole-trimethoprim, chloramphenicol, aminoglycosides, fluoroquinolones, tetracyclines, and aminoglycosides. Due to the predominance of such multidrug-resistant strains, the use of beta-lactam and other antibiotics is therefore restricted, which is problematic for the healthcare system because it forces doctors to recommend expensive drugs like carbapenems and limits the use of broad-spectrum antibiotics (Sehgal et al., 2007).

Due to the overuse of β-lactam antibiotics on plasmids, β-lactamases have been mobilized. Gram-negative bacteria developed enzymes like TEM-1 and SHV-1 to encounter a broad spectrum of first- and second-generation cephalosporins. TEM and SHV variants had amino acid alterations that changed their substrate profile to incorporate cephalosporins with an enlarged spectrum. Currently, in addition to these two enzymes, CTX-M-type enzymes are predominant. The most prevalent ESBL type is the CTX-M-15 variety, which also predominates globally. CTX-M-14 and CTX-M-27 are emerging in several regions of the world. The ESBL genes are present on plasmids and protected by transposons or insertion sequences, which allow their enzymatic spread (Castanheira et al., 2021).

From the analysis of the overall concept of neonatal sepsis, this article is prepared reviewing the facts of clinical manifestation, prevalence of infections and mother

related attribution, most common ESBL producing bacteria those are causing massive antibiotics resistance and mortality rate associated with neonatal sepsis focusing South Asiatic region particularly.

CHAPTER-2

Data Mining Methodology

An integrative review of literature on neonatal sepsis was conducted using keywords, such as, Neonatal, sepsis, South Asia, prevalent infection, (ESBL) AND (PREVALENCE) AND (SEPSIS) AND (ASIA), septicaemia, in sites like, NCBI, Google Scholar, Science Direct, BMC and PubMed using mesh term.

CHAPTER-3

Clinical manifestation and bacterial causative agents

Neonatal sepsis presents a complex scenario with its clinical manifestations closely tied to causative organisms. *Escherichia coli*, *Klebsiella pneumoniae,* and Coagulase-negative *Staphylococcus* (CoNS), mostly gram-negative bacteria, are the most frequent causes of neonatal late-onset sepsis (LOS). Particularly, antibiotic resistance is a major problem with *K. Pneumoniae* exhibiting high resistance levels against vital antibiotics like cefazolin and ceftazidime, particularly impacting third generation cephalosporins. Tragically, a 16.8% mortality rate in LOS cases underscores the severity of the condition, with predictors like low birth weight, respiratory distress, and convulsions influencing outcomes (Pan et al., 2020). Shifting focus to early-onset sepsis (EOS), 9.6% of neonates were suspected, of which 5.0% were culture-proven sepsis cases among neonatal admissions. An overwhelming majority of these cases (90.4%) gram-negative bacteria, mainly *E. coli* and *K. pneumoniae*, were held accountable for infections. Antibiotic administration patterns vary, with ampicillin/amoxicillin and amikacin in culture-equipped hospitals and third generation cephalosporins in facilities without culture capabilities. The duration of antibiotic treatment also differs based on

culture status, with culture-proven EOS requiring 19 days of treatment, compared to 9 days for culture-negative EOS (Salsabila et al., 2022). The years 2016-2018 saw a considerable neonatal sepsis burden, comprising 14.1% of admissions. Sepsis with early and late onsets had equal occurrence rates, culminating in an 18.1% case fatality rate. Culture-negative sepsis, accounting for 44% of cases, exhibited comparable mortality rates to culture-proven cases. Key pathogens include coagulase-negative *Staphylococci, Klebsiella pneumoniae,* and *Acinetobacter spp*., reflecting a concerning prevalence of multidrug-resistant bacteria with resistance rates as high as 62.6%, especially against extended-spectrum cephalosporins and carbapenems (Karmila et al., 2022). Clinical presentations of sepsis encompass lethargy, respiratory distress and hypothermia, while risk factors, those are remarkable for mortality encompass male neonates, low birth weight, and various clinical indications for instance, hypothermia, respiratory distress, and convulsions. Furthermore, independent predictors of mortality include gestational age, weight, age at admission, and various clinical parameters, underlining the complexity of neonatal sepsis outcomes (Karmila et al., 2022).

Causative bacterial agents—Coagulase-negative *Staphylococci, Klebsiella* s*pp*., and *Escherichia coli*—coupled with associated risk factors, provide a crucial framework to mitigate the death rate from infant sepsis in low- and middle-income nations. Hospital protocols for sepsis screening, including blood counts and C-reactive protein levels, guide diagnosis. Specific clinical indications like hypothermia, respiratory distress, and convulsions, along with certain bacterial agents, contribute to neonatal sepsis's diagnostic landscape (Karmila et al., 2022).

Furthermore, premature birth, maternal history of a urethral infection, and particular APGAR (appearance, pulse, grimace, activity, respiration) scores appear as major risk factors for newborn sepsis, emphasizing the significance of maternal health. Sepsis has many different manifestations, as seen by the frequency of newborn sepsis in NICUs, maternal and neonatal risk factors and different prevalence rates of early-onset and late-onset sepsis. Case mortality and incidence rates for cases with a clinical diagnosis and a confirmed culture bring awareness to the severity of neonatal sepsis (Rafi et al., 2020).

The masculine gender of neonate, extremely underweight while birth and poor Apgar scores exceptionally contributes to higher case-fatality rates in early-onset clinical sepsis. Birth weight distinctions manifest significantly in LOS cases, while Methicillin-resistant *Staphylococcus aureus* (MRSA) assumes prominence among pathogens. Center-specific differences in incidence rates underline the variable nature of the condition (Shin et al., 2009).

The intrusion of preterm newborns to severe bacterial infections due to their underdeveloped immune systems poses a substantial risk, potentially 500 to 1000 fold high in rate than term-newborns (Popescu et al.,2020). Transitioning to further research, studies on serum troponin and lactate levels provide insights into potential associations with mortality and increased mortality risk, respectively. These findings broaden our understanding of neonatal sepsis and emphasize the importance of tailored care strategies to mitigate its impact.

CHAPTER-4

Most prevalent neonatal infections in South Asia

Neonatal infections are a significant health concern in South Asia, particularly in countries like Bangladesh, infants who were admitted to the Neonatal Intensive Care Unit (NICU) report a greater rate of neonatal sepsis in public institutions. Conditions like; meningitis, bloodstream infections, and pneumonia are all included in this infection. Unfortunately, such infections are to blame for 1.6 million neonatal fatalities annually; astonishingly, 99 percent of them occur in developing nations. In South Asia, where it was responsible for 38.9% of all newborn fatalities in 2013, this issue is marked to be especially severe (Nyma et al., 2020). Of the 2,509 newborns, 242 cases (9.6%) were suspected to have EOS, and 83 cases (5.0% of neonatal) had sepsis that was confirmed by culture. Gram-negative bacteria made up many of the pathogenic organisms (85/94; 90.4%) (Salsabila et al., 2022).

A closer examination of the causes and consequences of neonatal sepsis reveals its devastating impact. Among the causes of clinically severe infections, bacterial attribution surpasses viral attribution, with bacterial infections displaying distinct clinical markers such as hypothermia, reduced movement, seizures, and difficulty eating (Arvay et al., 2022). Common bacteria for instance; *Escherichia coli* and Group B *streptococcus* are bacteria that often can lead to infections like sepsis, pneumonia, and meningitis. Other sources possibly could be viruses accountable for infection that include *Herpes Simplex Viruses, HIV,* and *Cytomegalovirus* (CMV). In the realm of viral agents, *Herpes simplex viruses, HIV, CMV,* and *Hepatitis B* pose notable threats (Neonatal Infections - Johns Hopkins All Children's Hospital, n.d.).

HIV and hepatitis B can be transferred intrapartum through contact with an infected birth canal or, if delivery is postponed after membrane rupture, by ascending infection. Transplacental transmission of these viruses is less prevalent. CMV frequently spreads transplacentally. Group B S*treptococci,* enteric gram-negative bacteria (mainly *Escherichia coli, Listeria monocytogenes, Gonococci,* and C*hlamydiae* are examples of

bacterial agents. *Rubella, toxoplasma, CMV, syphilis, and Zika* virus are examples of common infectious organisms that are spread transplacentally. Less frequently, viruses like HIV and hepatitis B are transferred transplacentally. The transit through an contaminated birth canal infected with herpes simplex viruses, HIV, hepatitis B, group B streptococci, enteric gram-negative organisms (mainly *Escherichia coli*), *Listeria monocytogenes, Gonococci* and *chlamydiae*. is typically the source of neonatal infections (Antibiotics in Neonates - Pediatrics, n.d.).

Breastfeeding within the first hour of birth has been found to reduce the risk of infection significantly. Sadly, in South Asia, only 50% of babies start nursing within this critical time frame. The significance of addressing this neonatal sepsis issue crucial because it is responsible for over 65% of neonatal deaths in South Asia, with a particularly high impact on babies within the first 6 days of life (M. K. Lee & Binns, 2020). Inadequate access to proper medical care and hygiene, along with the prevalence of infections, contribute to this concerning scenario. Efforts to combat neonatal infections have shown progress, but there is still much to be done. While diarrhea and acute respiratory infections continue to cause many child deaths in South Asia, interventions have reduced their impact. However, neonatal infections remain a neglected public health concern, responsible for a significant portion of neonatal mortality. The region witnesses a neonatal fatality rate of 46.3 per 1000 live births, with infections contributing to 30–40% of these deaths. In India alone, neonatal infections lead to 300,000 to 400,000 deaths annually. This emphasizes the urgent need for improved strategies to prevent and manage these infections, as they pose a serious threat to the health of newborns in South Asia (Zaidi et al., 2004).

Emergence of ESBL producing bacteria in neonatal sepsis

ESBL goes for extended spectrum beta-lactamase which is an enzyme generated by certain bacteria strains. Because the enzymes of bacteria hydrolyse most penicillin and cephalosporins, including oxyimino- β-lactam compounds. Antibiotics are often failed to resist ESBL-producing bacteria because they are capable of producing beta lactamase enzyme to inhibit the beta lactam ring in beta lactam antibiotics. In addition to being resistant to **β**-lactam antibiotics, such as third generation cephalosporins, ESBL-producing isolates frequently show resistance to other drug classes, including aminoglycosides, cotrimoxazole, and tetracycline (Chandel et al., 2011).

Klebsiella isolates, *Enterobacter* strains, and *Escherichia coli* strains are often reported gram-negative bacteria (GNB) in ESBL prevalence; coagulase *negative Staphylococci, group B streptococci,* and *Pseudomonas aeruginosa* are uncommon. The fact that ESBLs are plasmid-associated and the plasmids can interchange with several bacterial species is what makes them so vulnerable. Additionally, these plasmids have the capacity to carry co-resistance genes to helpful antibiotics such aminoglycosides, fluoroquinolones, tetracyclines, chloramphenicol, and sulfamethoxazole-trimethoprim. Because of this, the use of beta-lactam and other antibiotics is restricted due to the prevalence of such multidrug-resistant strains, which is bad for the health system because it forces doctors to prescribe costly medications like carbapenems and restricts the use of broad-spectrum antibiotics. The TEM-1 and SHV-1 enzymes originated in Gram-negative bacteria. TEM and SHV variants had amino acid changes that changed their substrate profile to incorporate cephalosporins with an enlarged spectrum. Currently, in addition to these two enzymes, CTX-M-type enzymes are predominant. The most prevalent ESBL type is the CTX-M-15 variety, which also predominates globally. CTX-M-14 and CTX-M-27 are emerging in several regions of the world.

According to previous study, ESBL-producing Enterobacteriaceae (ESBL-E) carriage rates in newborns and children were 74% and 59%, respectively. On the other hand,

ESBLs are most frequently found in *K. pneumoniae*, and ESBL-KP in neonates is a more significant cause of healthcare associated infection and is consequently associated with sepsis. This study could be utilized to demonstrate that the length of time infants spent in the NICU, recognized risk factor in the preterm population, is one of the major causes of neonatal infection (X. Li et al.,2017).

A study of 17 studies including a total of 40,644 people was carried out to figure out more about community-acquired bacteremia in South and Southeast Asia. Here, pathogenic organisms were found in 1722 (7%) cases out of 26,258 children. The most prevalent type of identified bacterial pathogen was *Salmonella enterica* serotype Typhi. *Streptococcus pneumoniae* and *Haemophilus influenzae* were also often isolated in children, likely because of the lack of widespread vaccination. Nearly 2% of EOS cases in China caused by group *B streptococci* that mostly ESBL producing. Gram-negative bacteria (GNB), such *as E. coli* (20.3%), and coagulase-negative *Staphylococci* (CoNS) (16.5%), are the other primary pathogenic bacteria that are frequently discovered in EOS also frequent in producing extended spectrum of beta lactamase (Dong et al., 2020). In the Asian Pacific region, Japan, Taiwan, the Philippines, Malaysia, and Singapore, respectively, reported prevalence rates of *Klebsiella* able to produce ESBL are 5%, 21.7%, 31%, and 38%. Additionally, within a single region, the prevalence of *E. coli* that produces ESBLs ranges from 6% to 23%. Neonatal ESBL production rates in *K. pneumoniae* and *E. coli* range from 11.8% to 100% across different nations (Chandel et al., 2011a).

Analysis of recent systematic studies:

In healthy adults and children, faecal colonisation with ESBLs is predicted to occur in 14% of cases worldwide, with a greater frequency of 22% in Southeast Asia, subjected to a recent systematic scrutinized view and meta-analysis. Travellers coming from South Asia had high levels of ESBL-producing Enterobacteriaceae colonisation. ESBL-producing *E. coli* infections in the population have been reported in numerous nations. An increase in the prevalence of ESBL-producing organisms was observed in recent

prospective observational research conducted in the United States; community-acquired ESBL producers were shown to be responsible for 36.8% of all ESBL infections. In healthy adults and children worldwide, fecal colonization with ESBLs is anticipated to occur in 14% of cases, with a higher incidence of 22% in Southeast Asia, according to a current systematic review and meta-analysis (Dolma et al., 2018).

A total of 1738 infants were registered in the trial and examined for sepsis signs and symptoms over the course throughout the three-year research phase (2002–2005) in India. *Salmonella* species (>8%), *Klebsiella* species (>50%), and *E. coli* (60%), all of which are promoted by high levels of co-resistance to aminoglycosides and fluoroquinolones, are frequently discovered ESBL generating GNB phenotypes. Furthermore, substantial colonisation of the NICU by *K. pneumoniae* that produces ESBLs and evidence that these infections are transmitted to newborns by medical personnel were found. By investigating the disc synergy of CTX and CAZ in the presence and absence of clavulanic acid, it was possible to confirm the presence of ESBL activity in *E. Coli* and *Klebsiella* (Chandel et al., 2011).

A retrospective investigation in southern China demonstrated the effectiveness of carbapenem and fluoroquinolones against ESBL-producing bacteria. Additionally, usage of third-generation cephalosporin in previous time, preterm underweight while birth, and extended mechanical ventilation (7 days) are risk factors for ESBL-producing *E. coli* and *K. pneumoniae*. Most ESBL-producing microbes are resistant to a variety of antibiotics. According to reports, infections occurring by ESBL-producing bacteria are greater common when third generation cephalosporins are used. 19 (0.81%) of the 2,358 newborns, patients from NICU throughout the study period had ESBL-producing *K. pneumoniae* infections and 3 (0.13%) had ESBL-producing *E. coli* infections. Five (0.21%) and twelve (0.51%) of the infections were caused by non-ESBL-producing *E. Coli and K. pneumoniae*, respectively. They all met the requirements for infection. 19 (86.4%) out of 22 patients with ESBL-producing bacterial infections had *K. pneumoniae* infections, while 3 (13.6%) had *E. coli* infections (Huang et al., 2007).

The BARNARDS network, which comprises of 12 clinical sites dispersed throughout 7 LMICs in Africa and south Asia, aims to assess the incidence, prevalence, risk factors, bacterial aetiology, and burden of antibiotic resistance in newborn sepsis. Researchers identified common Gram-negative bacteria (GNBs) containing carbapenemase genes using whole-genome sequencing (WGS), describing particular variations and plasmid types throughout the various study platforms. South Asian countries had a greater prevalence of all the ESBL-indicating genes, such as blaCTX-M-15, 34.7% blaNDM, and 8.0% blaOXA-48-like genes (63.0%). There are numerous blaOXA-48-like genes, and curiously, a higher incidence of blaNDM than previously reported was discovered in Pakistan, India, and Bangladesh. Through the first 14 days of life, Asian samples showed a consistent decline in the prevalence of blaNDM (53.7% to 27.7%) and blaOXA-48-like genes (35.4% to 0%), independent of the method of delivery or sepsis outcome (Carvalho et al., 2022).

Most of the isolates from all the trials exhibited extensive antibiotic resistance. 98% of *Klebsiella* and 81% of *E. coli* cases had high levels of AMP resistance, whilst other GNB had complete AMP resistance. Additionally, *Klebsiella and E. coli* showed enhanced resistance to CIP (35%), AMC and GEN (50% each). The resistance of Enterobacter species to the ESBL inhibitor AMC among the other GNB was shockingly high (.95%). However, more than 50% of *E. coli* (11/21) and 46% of *Klebsiella* species (52/113) exhibited complete resistance to all three third generation cephalosporins. A high level of resistance to third generation cephalosporins was also detected in other GNB (mainly *Enterobacter* species) of 75% (Chandel et al., 2011).

Tabular Presentation of Prevalence of Beta Lactam antibiotic resistance and Prevalence of ESBL genes

Ref.	Study Details (M/F, Participant numbers)	Prevalence of Beta Lactam antibiotic resistance	Prevalence of ESBL genes
(Carvalho et al., 2022)	BARNARDS is a network of 12 clinical platforms across 7 LMICs in Africa and south Asia (M/F Not Identified)	third generation cephalosporins, aminoglycosides, cotrimoxazole, tetracycline and fluoroquinolones.	(63.0%) ex. blaCTX-M-15, 34.7% blaNDM and 8.0% blaOXA-48-like genes) The blaOXA-48-like genes have allegedly vast spread throughout south Asia. (35.4% to 0%)
(Chandel et al., 2011)	A total of 85 47% of the patients were male, and 53% were female.	Augmentin, clavulanic acid, ceftazidime	Mutation of gene On plasmids,-1 and SHV-1 resulted in alteration
(Ding et al., 2019)	newborns aged 0-30 days. M/F not identified	Carbapenems, fosfomycin,	NDM-1 was the most common carbapenem-resistant genotype (81.0%, 17/21).
(Russell et al., 2023)	423 peripartum women (might transmit in neonate, causing sepsis)	Commonly used multidrug resistant.	blaCTX-M-15 (41.5%), blaCTX-M-55 (24.8%), and blaCTX-M-27 (15.1%).
(Oktaviani Sulikah et al., 2022)	swab samples from rectal 200 pregnant women (might transmit in neonate, causing sepsis)		$bla_{CTX\text{-}M\text{-}15}$ was the most prevalent type of ESBL gene

Antimicrobial resistance associated challenges in treatment.

Antimicrobial resistance (AMR), an increasing threat, warrants special consideration. AMR was projected to be responsible for 214,500 deaths in neonates, data from the five countries (India, Nigeria, the Democratic Republic of the Congo, Pakistan, and China), which together accounted for more than 50% death in neonates due to sepsis. Indeed, according to some reports, gram-negative bacteria are resistant to up to 80% for first-line antibiotics. 63% of gram-negative organisms were most prevalent among isolates from hospital settings where n=24 273), where top three are *Klebsiella spp* (23%), *Escherichia coli* (14%), and *Acinetobacter spp* (8%). *Staphylococcus aureus* and Coagulase-negative *Staphylococci* made up most of the Gram-positive organisms (20% and 9%, respectively). In comparison to Gram positive organisms the Gram-negative organisms identified to have a link to a higher case fatality rate. The DeNIS partnership examined newborns delivered in India's tertiary care facilities. High rates of multidrug resistance were found in *Acinetobacter, Klebsiella* species, and *E. coli* isolates from infants suspected of having sepsis (82%, 54%, and 38%, respectively)(Popescu et al., 2020).It was evident that 54% of isolated bacteria were resistant to at least one antibiotic from among four to six classes of antibiotics, and we found that GNB causing newborn sepsis in LMICs frequently carried both resistance genes and virulence factors(Sands et al., 2021).

Broad-spectrum antibiotic exposure may potentially limit the child's future treatment options. In addition to AMR-related impacts, needless antibiotic exposure may have less obvious negative effects, such as early gut microbiota alterations that increase the risk of developing allergy illness (Popescu et al., 2020). Although, the 2016 WHO12 update on empiric antibiotics for newborn sepsis advises using ampicillin with gentamicin as first-line therapy, only 28.5% of gram-negative isolates were sensitive to this regimen in the sub study. Other combinations, including ceftazidime-amikacin, had susceptibility rates that were three times greater. Additionally, ampicillin-gentamicin treatment was linked to higher mortality than ceftazidime-amikacin treatment. The extreme rarity of ampicillin susceptibility in Gram-negative and *Staphylococcus spp.*

infections raises doubts about the necessity of ampicillin as a cornerstone of newborn sepsis treatment regimens. A study delacred,56 out of 390 Gram-negative isolates, or 14.4%, were resistant to meropenem. This is concerning because *Klebsiella* spp., a prominent cause of early-onset newborn sepsis in LMICs, often develop resistance to meropenem (Schlapbach et al., 2021). In the human microbiota, antibiotic resistance genes regularly circulate between bacteria, and the gut bacterial focal point for horizontal gene transfer.Since colonization with multi-drug resistant (MDR) bacteria is a prelude to invasive infections like those that cause sepsis, this is specifically alarming for the neonatal population (Carvalho et al., 2022).

Analysis of different studies for treatment challenges with antibiotics

Neonates presenting with suspected sepsis aged 0 to 60 days were enrolled in the main BARNARDS research at BARNARDS hospital locations in Bangladesh, Ethiopia, South Africa, India, Pakistan, Nigeria, Rwanda from the time period 11 November 2015 to 31 March 2018.Study showed 1019 had accessible data on antibiotics and sepsis with culture support and had received one of the four most typical treatments prescription antibiotic mixtures include ampicillin and gentamicin. Particularly to be mentioned mixtures like, Piperacillin-tazobactam-amikacin, Ceftazidime-Amikacin, or acetaminophen-amikacin-clavulanate (Schlapbach et al., 2021). The team, which included scientists from Kolkata's ICMR-National Institute of Cholera and Enteric Diseases, identified 57 bacterium species that become resistant to most antibiotics. Bacteria harbouring carbapenemase genes exhibited antibiotic resistance to amoxicillin, imipenem, and ertapenem, according to antibiotic resistance profiles. *Escherichia coli, Klebsiella pneumonia,* and *Enterobacter cloacae* were the three predominant species that had the genes for antibiotic resistance. The bacteria were passed from mother to infant or from one newborn to another. During the first two weeks following birth, sepsis-affected infants showed greater percentages of genes associated with antibiotic resistance (Nature Publishing Group, 2022). Another analysis done with of 12 622 births at For 60 days, the state of Odisha was monitored at home. 842 patients with suspected sepsis were admitted with the condition, 95% of whom

were between 4 and 60 days old. Cases of suspected sepsis were transferred to study hospitals for further assessment, including blood cultures. Sepsis incidence determined by culture was 6.7/1000 newborns, with 26% Gram positives (mostly *Staphylococcus aureus)* and 51% Gram negatives (*Klebsiella* predominating). The discovery of a very high degree of penicillin and ampicillin resistance signals a significant obstacle in administering the medication. Additionally, it was shown that there was only very little resistance to Gentamicin and Amikacin and moderate resistance to cephalosporins (Panigrahi et al., 2017).

In a lower middle-income country like Bangladesh, dense places like slums in Dhaka, a lack of access to clean water for drinking, a lack of basic hygienic infrastructure, and the misuse of locally produced, inexpensive, and perhaps subpar antimicrobial medications that are easily available over the counter. This atmosphere is perfect for the rapid spread of antimicrobial resistance across the populace and environment. In India, comparable instances have been reported (Islam et al., 2014). To assess the spread of resistance and hazards to public health, a prospective surveillance in the general population and environment is required. Therefore, it is crucial to have trustworthy tools to help determine the course of treatment and to stop giving it as soon as it is thought to be safe for the child (Sands et al., 2021).

Mortality rate among neonates

The incidence of severe sepsis is higher in underdeveloped nations and is linked to a very high case-fatality rate. Over half of the projected 6.3 million fatalities of children under the age of five globally were attributed to sepsis, and many of these deaths occurred in Asia. Pneumonia was responsible for 15% of these deaths. 40- 41% (3.6 million) of all deaths in children under the age of five occur during the newborn period each year. Most of these fatalities take place in low-income nations, and about 1 million of them are caused by infectious diseases, including neonatal sepsis. Even in 2022, sepsis continued to be a major killer, accounting for 19.7% of all fatalities worldwide (Zaidi et al., 2011). There are, however, few studies on sepsis coming from Southeast

Asia. 56% of youngsters in this region were found to have severe sepsis, according to recent research. Overall sepsis-related death rates were reported to be about 39.3% and 37%, respectively, in Nepal and Bangladesh (Mehta et al., 2022).

According to the National Neonatal-Perinatal Database 1997, sepsis is still the main cause of illness and mortality in the community for Indian neonates. Microbiological characteristics are not well understood in this population. (Chandel et al.,2011) The death rate of newborn sepsis among outborns was 38.24%, according to a 1-year prospective research. Around 2.6 million people died during the neonatal era in 2016, with India accounting for 24% of all newborn fatalities worldwide and having a neonatal mortality rate of 25.4 per 1000 live births, with 30% of mortality cases resulting from infections and sepsis (Meshram et al., 2019). The Cochrane Central Register of Controlled Trials was searched as a data source between January 1, 2004, and November 16, 2020.The pooled estimates of 86 out of 106 children with sepsis, severe sepsis, and septic shock strongly support higher mortality. The odds ratio for categorical variables such as pediatrics logistic organ dysfunction, degree of consciousness, etc., and the mean difference for continuous variables such as oncological facts and severe acute malnutrition are estimated by a pooled sample of data.(Menon and others, 2022) The INDICAP study for ICU newborns in 2022 provided additional evidence that sepsis impacted 65% of ICU patients in India, with a 25% fatality rate, making India the Southeast Asian country with the second-highest sepsis mortality (Mehta et al., 2022).

According to more recent studies, sepsis in the general population is responsible for roughly 40% of neonatal fatalities (National Neonatology Forum NNPD Network, 2005). BBS and RKL are in the eastern, very resource-poor state of Orissa, which has one of India's highest rates of newborn and infant mortality. Low birth weight babies, another important cause of morbidity and hospital admission in India, have a considerably greater prevalence of neonatal sepsis among hospital-born newborns. Only studies conducted in hospitals have described the microbiology of neonatal infections, and in these investigations, infections caused by Gram-negative bacilli

(GNB) that produce extended-spectrum b-lactamases (ESBL) have been linked to greater mortality. In patients who report with ESBL-positive infections, the increased mortality is typically thought to be related to higher rates of treatment failure rather than an increase in disease severity (Chandel et al.,2011). A study done in China with 85 patients offers strong support for this assertion. It was discovered that 25 percent of patients (or 21 patients) died in hospitals and that improper antibiotic delivery was associated with treatment failure. Additionally, using the incorrect medications to bacteremic patients could significantly raise their mortality rate. Neonatal sepsis was predicted to occur in China at a rate of 25.6 per 1000 live births, according to birth population-based surveys from one region that roughly matched national average levels. Based on population-level research conducted over the previous 20 years, the global incidence of neonatal sepsis was estimated to be 2202 per 100,000 live births (LBs), with death ranging from 11% to 19%. In China, the case fatality rate for EOS was 19% (Dong et al., 2020).

According to a recent study from 2019, 27% of neonates who had sepsis that was suspected or confirmed failed immunotherapy trials that were attempted on 74 potentially eligible articles. In five separate nodes of a meta-analysis, the effects of immunotherapies such G-CSF, GM-CSF, IgG, and IgGM were contrasted with those of a placebo. According to the proposed pooled effects, none of the interventions could demonstrate statistically significant differences from placebo to reduce the neonate all-cause mortality rate. However, the mortality rate was lowered because of GM-CSF's top rating of 76.2%. Nevertheless, certain immunotherapies could not have a significant reduction in mortality because of patient-specific factors, such as the immunological condition of babies (Li et al., 2019).

Mother associated risk factors

Increased risks of maternal sepsis were linked to several maternal traits. Maternal sepsis is usually linked to both obstetric and non-obstetric illnesses. Maternal sepsis has a 55.03% positive predictive value for preterm delivery. Babies born to mothers who had

sepsis were more likely to experience newborn problems, such as neonatal shock. It has been frequently demonstrated that breastfeeding lowers the incidence of newborn sepsis. Equivalent advantages for immunomodulation may potentially arise when maternal colostrum is administered orally to extremely low birth weight infants in the oropharyngeal region, although additional research in low and middle-income countries (LMIC) remains necessary. A meta-analysis of 18 clinical trials involving 4062 newborns revealed that the use of probiotics lowered the risk of late onset neonatal sepsis by 20% when compared to taking no action (Popescu et al., 2020).

Following childbirth, the umbilical cord often becomes a location prone to bacterial contamination and subsequent infections, particularly in countries where traditional cord-care practices and challenges with maintaining sterility are prevalent. In between hospitals and communities, as well as between nations, studies' recommendations for umbilical cord care differ greatly. In comparison to mothers and infants from African nations, south Asian mothers and infants had a higher prevalence of all the antibiotic resistant genes that might lead to neonatal sepsis. This may happen during or after labour, via the mother's vaginal or gut bacteria, potentially leading to neonatal sepsis (Nature Publishing Group, 2022).

According to the researchers, inadequate hand hygiene, antibiotic usage, and previous infections likely played a role in the transmission of antibiotic resistance genes within gut bacteria (Ozarslan et al., 2023). In this context, the primary focus has been on preventing infections using antiseptics, antibiotics, soap and water, dry cord care, and handwashing. The application of 4% chlorhexidine daily for one week after home delivery in low-income settings or as a substitute for unsafe traditional remedies led to a reduction in infection and mortality rates by 23-56% and 23%, respectively, in LMIC communities (Popescu et al., 2020) As a result, the World Health Organization (WHO) adjusted its recommendations accordingly (Carvalho et al., 2022).

Compared to neonates delivered to moms who did not have a prenatal urinary tract infection, those born to mothers who did, had a 3.55 times higher risk of developing

neonatal sepsis (Nature Publishing Group, 2022). Furthermore, infants born to mothers who had experienced intrapartum fever had a 3.63-fold higher likelihood of developing neonatal sepsis compared to infants born to mothers without intrapartum fever (Bayih et al., 2021). All the cases had their maternal records examined, and among them, 30 (28.85%) had been administered intrapartum antibiotics. Of the 104 mothers who received intrapartum antibiotics, 54 (51.92%) delivered prematurely (<37 weeks), and 50 (48.08%) delivered at term (>37 weeks), yet both groups experienced cases of neonatal sepsis (N.-C. Lee et al., 2004). Research indicates that premature birth significantly influences the diversity and composition of species in the first months of life, leading to an increase in *E. Coli, E. cloacae, and Klebsiella spp.* (Carvalho et al., 2022).

Moreover, neonatal gut microbiota composition and development are influenced by the vaginal and rectal microbiotas of the mother at delivery as well as the clinical and social environment later. Antibiotic use disrupts the gut microbiota and can alter bacterial populations that have a detrimental effect on newborn development. Generally used antibiotics are frequently beta-lactams due to availability and cost (Carvalho et al., 2022).

Preventive measures and health care challenges

The landscape of healthcare is riddled with critical challenges, chief among them being the ominous presence of neonatal sepsis. This condition, responsible for a substantial toll on morbidity and mortality, particularly in countries like China, demands a multifaceted approach. Understanding the intricacies of neonatal sepsis, including its epidemiology, pathogen profiles, and effective treatment strategies, is paramount for optimizing neonatal healthcare outcomes (Dong et al., 2020). Studies have indicated a noteworthy finding regarding potential differences in the occurrence of neonatal early-onset sepsis (EOS) and the involvement of *Group B Streptococcus* (GBS) as a causative agent in China when compared to more advanced countries. These distinctions could be linked to variances in population attributes and healthcare practices during childbirth

and the postnatal period. Therefore, there is a need for increased research and discussion on GBS screening and the use of antibiotics during childbirth in China (Wu et al., 2009).

The imperative for preventive measures against these healthcare challenges is clear. A vigilant approach entails close monitoring of local neonatal sepsis epidemiology within each institution, coupled with regular surveillance of pathogens, antimicrobial resistance patterns, and treatment outcomes. This data-driven strategy informs clinical practices and guides the implementation of preventive measures (Ocviyanti & Wahono, 2018). Additionally, swift and comprehensive infectious workups are crucial for accurate diagnosis. Proper collection and processing of specimens for culture, along with consideration of viral pathogens as potential culprits for late-onset sepsis, are key facets of this approach (Salsabila et al., 2022).

Moving to Nepal, neonatal sepsis emerges as a significant contributor to mortality in neonatal intensive care units (NICUs) of developing nations. This issue, commanding the attention of neonatologists, underscores the importance of understanding the bacteriological profile of neonatal sepsis. Informed management strategies rely on the identification of bacteria types and their antibiotic susceptibility patterns (Pokhrel et al., 2018). Preventive measures rise to meet these challenges, urging for the implementation of systematic surveillance of bacteriological profiles and antibiotic susceptibility patterns. This approach aids healthcare professionals in staying ahead of emerging antibiotic resistance trends, allowing for the necessary adaptation of treatment protocols. Further bolstering the defences are strict infection prevention and control measures within NICUs. These measures encompass practices such as maintaining impeccable hand hygiene, following aseptic techniques during medical procedures, and ensuring thorough sterilization of equipment (Al-Matary et al., 2019). Parallelly, complications associated with Prolonged Rupture of Membranes (PROM) demand attention. High maternal and perinatal morbidity and mortality risks are linked to PROM, which occurs in a notable percentage of pregnancies. The risk of neonatal sepsis rapidly increases with prolonged membrane rupture. Neonatal sepsis, particularly in cases of PROM, poses an imminent threat to the health and survival of newborns,

necessitating timely interventions. Addressing these challenges necessitates the prompt identification and management of PROM, closely monitoring pregnant women with this condition, and initiating appropriate interventions as guided by established protocols. The adoption of infection prevention measures further contributes to mitigating risks. This approach involves rigorous hygiene practices during vaginal examinations, minimizing invasive procedures, and ensuring a sterile environment during labor and delivery (Ocviyanti & Wahono, 2018).

The continuum of healthcare challenges extends globally. Accurate tracking of pathogen trends is pivotal to mount effective interventions against neonatal sepsis. The emergence of antibiotic resistance, especially among gram-negative bacteria like *Burkholderia cepacia*, compounds the management challenges. This issue is exemplified in studies revealing its prevalence in both early-onset and late-onset sepsis cases in Sana'a, Yemen (Salah et al., 2021). The spectrum of preventive measures encompasses the fortification of surveillance systems to monitor incidence, pathogen dynamics, and antibiotic resistance trends. Equally important is the implementation of infection prevention and control measures in neonatal units, underscoring the importance of meticulous hygiene practices, aseptic techniques, and a pristine environment (Toan et al., 2022). Further unravelling the complexity of neonatal sepsis, understanding the risk factors, microbial profiles, and complications assumes center stage. Delineating between early-onset and late-onset sepsis, and comprehending the causative organisms and their respective factors, is a cornerstone of effective prevention. Early detection and diagnosis, guided by protocols and guidelines, converge with rigorous infection prevention and control practices in NICUs to create a fortified defence. This multi-pronged approach mandates educating healthcare providers, deploying diagnostic tools judiciously, and fostering a culture of hygiene and disinfection.

In Chinese NICUs, challenges encompass the need for improved care practices for very preterm infants (VPIs), such as antenatal corticosteroids and tailored interventions. Preventive measures pivot around evidence-based guidelines, comprehensive quality

improvement efforts, and optimized neonatal care practices (Cao et al., 2021). Similarly, the intricate interplay between early-onset sepsis (EOS) and antibiotic usage in NICUs necessitates strengthening diagnostic capabilities. This entails enhanced access to diagnostic tools and adherence to established criteria, supplemented by antimicrobial stewardship programs. Culture-negative neonatal sepsis stands as another challenge, with elusive causative pathogens hindering accurate diagnosis and treatment. The prevalence of multidrug-resistant bacteria in neonatal sepsis adds another layer of complexity. Preventive measures rise to confront these challenges, emphasizing the development of advanced diagnostic techniques and the diligent implementation of antimicrobial stewardship programs. In low- and middle-income countries, the battle against neonatal sepsis takes center stage, with a spotlight on late-onset and hospital-acquired sepsis. Strengthening infection prevention and control practices within healthcare facilities, coupled with early recognition and diagnosis of neonatal sepsis, emerges as pivotal preventive strategies (Toan et al., 2022).

In the Indian context, a high neonatal mortality rate attributed to sepsis underscores the need for strengthened infection prevention and control practices. The implementation of antibiotic stewardship programs emerges as a crucial measure to optimise antibiotic usage (Pokhrel et al., 2018).

Ultimately, challenges to neonatal healthcare are met with a chorus of solutions, united by a common goal – to protect the vulnerable lives of newborns. Through meticulous surveillance, robust infection control measures, and informed treatment strategies, the healthcare community takes a united stand against the perils of neonatal sepsis, striving for healthier tomorrows (Karmila et al., 2022).

CHAPTER-5

Future Work

This paper may provide a quick overview of future updates to knowledge concerning neonatal sepsis. It is also undeniable that, despite more study being done, there is still little organised information about newborn sepsis in the South Asian region. Even so, we have compiled the most up-to-date information in this article while working on it, despite the restricted sources. As a result, it will be simple to find all the information compiled in one article that suits preferences.

Conclusion

Sepsis in newborns is a dangerous infection that can have devastating consequences for newborns. However,an increasing collection of research is available on efficient early diagnosis and treatment methods.The choice of antibiotics for empirical treatment of neonatal sepsis depends on several factors, including the age of the newborn, the clinical presentation, and the local epidemiology of resistant organisms. In general, it is recommended to take broad-spectrum antibiotics that work against both gram-positive and gram-negative bacteria. There are still a number of difficulties in the identification and management of neonatal sepsis.One of the biggest challenges is the emergence of antibiotic-resistant bacteria. This is marked as a particular problem in developing countries, where access to quality healthcare is limited and antibiotics are often misused. To address these challenges, there is a need for increased investment in research on neonatal sepsis, improved access to quality healthcare for pregnant women and newborns, and education and awareness raising. By addressing these challenges, we can create a future where neonatal sepsis is no longer a threat to the lives of newborns.

References:

- Al-Matary, A., Heena, H., AlSarheed, A. S., Ouda, W., Alshahrani, D., Wani, T. A., Qaraqei, M., & Abu-Shaheen, A. (2019). Characteristics of neonatal Sepsis at a tertiary care hospital in Saudi Arabia. Journal of Infection and Public Health, 12(5), 666–672. https://doi.org/10.1016/j.jiph.2019.03.007
- Arvay, M. L., Shang, N., Qazi, S., Darmstadt, G. L., Islam, M. S., Roth, D., Liu, A., Connor, N. E., Hossain, B., Rahman, Q. S., Arifeen, S. E., Mullany, L. C., Zaidi, A. K. M., Bhutta, Z. A., Soofi, S. B., Shafiq, Y., Baqui, A. H., Mitra, D. K., Panigrahi, P., . . . Schrag, S. J. (2022). Infectious aetiologies of neonatal illness in south Asia classified using WHO definitions: a primary analysis of the ANISA study. The Lancet Global Health, 10(9), e1289–e1297. https://doi.org/10.1016/s2214-109x(22)00244-3
- Bayih, W. A., Ayalew, M. Y., Chanie, E. S., Abate, B. B., Asnakew, S., Belay, D. M., Aynalem, Y. A., Sewyew, D. A., Kebede, S. D., Demis, A., Yitbarek, G. Y., Tassew, M. A., Birhane, B. M., & Alemu, A. Y. (2021). The burden of neonatal sepsis and its association with antenatal urinary tract infection and intra-partum fever among admitted neonates in Ethiopia: A systematic review and meta-analysis. Heliyon, 7(2), e06121. https://doi.org/10.1016/j.heliyon.2021.e06121
- Cao, Y., Jiang, S., Sun, J., Hei, M., Wang, L., Zhang, H., Ma, X., Wu, H., Li, X., Sun, H., Wei, Z., Shi, Y., Wang, Y., Gu, X., Yang, T., Lu, Y., Du, L., Chen, C., Lee, S. K., & Zhou, W. (2021). Assessment of neonatal intensive care unit practices, morbidity, and mortality among very preterm infants in China. JAMA Network Open, 4(8), e2118904. https://doi.org/10.1001/jamanetworkopen.2021.18904
- Carvalho, M. J., Sands, K., Thomson, K., Portal, E., Mathias, J., Milton, R., Gillespie, D., Dyer, C., Akpulu, C., Boostrom, I., Hogan, P. G., Saif, H., De Oliveira Ferreira, A. C. A., Nieto, M., Hender, T., Hood, K., Andrews, R., Watkins, W. J., Hassan, B., . . . Walsh, T. R. (2022). Antibiotic resistance genes

in the gut microbiota of mothers and linked neonates with or without sepsis from low- and middle-income countries. Nature Microbiology, 7(9), 1337–1347. https://doi.org/10.1038/s41564-022-01184-y

- Castanheira, M., Simner, P. J., & Bradford, P. A. (2021). Extended-spectrum **β**-lactamases: an update on their characteristics, epidemiology and detection. JAC-antimicrobial Resistance, 3(3). https://doi.org/10.1093/jacamr/dlab092
- Chandel, D. S., Johnson, J. A., Chaudhry, R., Sharma, N., Shinkre, N., Parida, S., Misra, P. R., & Panigrahi, P. (2011). Extended-spectrum β-lactamase-producing Gram-negative bacteria causing neonatal sepsis in India in rural and urban settings. Journal of Medical Microbiology, 60(4), 500–507. https://doi.org/10.1099/jmm.0.027375-0
- Chaurasia, S., Sivanandan, S., Agarwal, R., Ellis, S., Sharland, M., & Sankar, M. J. (2019). Neonatal sepsis in South Asia: huge burden and spiralling antimicrobial resistance. BMJ, k5314. https://doi.org/10.1136/bmj.k5314
- De Lauzanne, A., Sreng, N., Foucaud, E., Touch, S., Chon, T., Yem, C., Hak, V., Heng, S., Meng, S., Gouali, M., Nadimpalli, M., Inghammar, M., Rabenandrasana, M. a. N., Collard, J. M., Vray, M., Hello, S. L., Kerléguer, A., Piola, P., Delarocque-Astagneau, E., . . . Borand, L. (2022). Prevalence and factors associated with faecal carriage of extended-spectrum β-lactamase-producing Enterobacterales among peripartum women in the community in Cambodia. Journal of Antimicrobial Chemotherapy, 77(10), 2658–2666. https://doi.org/10.1093/jac/dkac224
- Dolma, K., Summerlin, T. L., Wongprasert, H., Lal, C. V., Philips, J. B., & Winter, L. (2018). Early-Onset Neonatal Sepsis with Extended Spectrum Beta-Lactamase Producing Escherichia Coli in Infants Born to South and South East Asian Immigrants: A Case Series. American Journal of Perinatology Reports, 08(04), e277–e279. https://doi.org/10.1055/s-0038-1675336

- Dong, Y., Basmaci, R., Titomanlio, L., Sun, B., & Mercier, J. (2020). Neonatal sepsis: within and beyond China. Chinese Medical Journal, 133(18), 2219–2228. https://doi.org/10.1097/cm9.0000000000000935
- Fleischmann, C., Reichert, F., Cassini, A., Horner, R., Harder, T., Markwart, R., Tröndle, M., Savova, Y., Kissoon, N., Schlattmann, P., Reinhart, K., Allegranzi, B., & Eckmanns, T. (2021). Global incidence and mortality of neonatal sepsis: a systematic review and meta-analysis. Archives of Disease in Childhood, 106(8), 745–752. https://doi.org/10.1136/archdischild-2020-320217
- For patients and families. (n.d.). Johns Hopkins Medicine. https://www.hopkinsmedicine.org/all-childrens-hospital/patient-families#:~:text=Group%20B%20Streptococcal%20Disease%20(GBS)&text=Group%20B%20streptococcus%20is%20a,sepsis%2C%20pneumonia%2C%20and%20meningitis.
- Huang, Y., Zhuang, S., & Du, M. (2007). Risk Factors of Nosocomial Infection with Extended-Spectrum Beta-Lactamase-Producing Bacteria in a Neonatal Intensive Care Unit in China. Infection, 35(5), 339–345. https://doi.org/10.1007/s15010-007-6356-9
- Islam, M. A., Nabi, A. N., Rahman, M., Islam, M. R., Ahmed, D., Faruque, A. S. G., Hossain, A., Van Belkum, A., & Endtz, H. P. (2014). Prevalence of faecal carriage of NDM-1-producing bacteria among patients with diarrhoea in Bangladesh. Journal of Medical Microbiology, 63(4), 620–622. https://doi.org/10.1099/jmm.0.064527-0
- Karmila, A., Barchia, I., Ramandati, A., & Zhang, L. (2022). Clinical and bacteriological profile of culture-negative and culture-proven neonatal sepsis in Palembang, Indonesia. Journal of Infection in Developing Countries, 16(12), 1887–1896. https://doi.org/10.3855/jidc.14638

- Lee, M. K., & Binns, C. (2019). Breastfeeding and the risk of infant illness in Asia: a review. International Journal of Environmental Research and Public Health, 17(1), 186. https://doi.org/10.3390/ijerph17010186
- Li, Y., Yang, S., Wang, G., Liu, M., Zhang, Z., Liu, H., Yu, K., & Wang, C. (2019). Effects of immunotherapy on mortality in neonates with suspected or proven sepsis: a systematic review and network meta-analysis. BMC Pediatrics, 19(1). https://doi.org/10.1186/s12887-019-1609-1
- Mehta, Y., Paul, R., Rabbani, R., Acharya, S. P., & Withanaarachchi, U. K. (2022). Sepsis management in Southeast Asia: A review and clinical experience. Journal of Clinical Medicine, 11(13), 3635. https://doi.org/10.3390/jcm11133635
- Meshram, R. M., Gajimwar, V. S., & Bhongade, S. (2019). Predictors of mortality in outborns with neonatal sepsis: A prospective observational study. The Nigerian Postgraduate Medical Journal, 26(4), 216. https://doi.org/10.4103/npmj.npmj_91_19
- Morioka, I., Morikawa, S., Miwa, A., Minami, H., Yoshii, K., Kugo, M., Kitsunezuka, Y., Enomoto, M., Jikimoto, T., Nakamura, M., Yokoyama, N., Nishio, H., Matsuo, M., & Yamada, H. (2012). Culture-Proven Neonatal sepsis in Japanese Neonatal Care units in 2006–2008. Neonatology, 102(1), 75–80. https://doi.org/10.1159/000337833
- Nature Publishing Group. (2022). Antibiotic resistance genes from mothers may trigger sepsis in newborns. Nature. https://doi.org/10.1038/d44151-022-00083-9
- Neonatal bacteremia in a neonatal intensive care unit: analysis of causative organisms and antimicrobial susceptibility. (2004, January 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/15077885/
- Nyma, Z., Rahman, M., Hasan, S., Roby, N. U., Khanam, F., Alam, E., & Ali, M. (2020). Prevalence and Associated Risk Factors of Sepsis among Neonates Admitted into Neonatal Intensive Care Units of Public Hospitals in Dhaka. Cureus. https://doi.org/10.7759/cureus.7461

- Ocviyanti, D., & Wahono, W. T. (2018). Risk Factors for Neonatal Sepsis in Pregnant Women with Premature Rupture of the Membrane. Journal of Pregnancy, 2018, 1–6. https://doi.org/10.1155/2018/4823404
- Ozarslan, N., Gaw, S. L., Cassidy, A. G., & Caughey, A. B. (2023). Predictors of antepartum maternal sepsis and effects on neonatal outcomes: a population-based cohort study. Journal of Perinatology, 43(6), 752–757. https://doi.org/10.1038/s41372-023-01696-3
- Pan, T., Zhu, Q., Li, P., Hua, J., & Feng, X. (2020). Late-onset neonatal sepsis in Suzhou, China. BMC Pediatrics, 20(1). https://doi.org/10.1186/s12887-020-02103-y
- Panigrahi, P., Chandel, D. S., Hansen, N. I., Sharma, N., Kandefer, S., Parida, S., Satpathy, R., Pradhan, L., Mohapatra, A., Mohapatra, S. S., Misra, P. R., Banaji, N., Johnson, J. A., Morris, J. G., Gewolb, I. H., & Chaudhry, R. (2017). Neonatal sepsis in rural India: timing, microbiology and antibiotic resistance in a population-based prospective study in the community setting. Journal of Perinatology, 37(8), 911–921. https://doi.org/10.1038/jp.2017.67
- Pokhrel, B., Koirala, T., Shah, G., Joshi, S., & Baral, P. (2018). Bacteriological profile and antibiotic susceptibility of neonatal sepsis in neonatal intensive care unit of a tertiary hospital in Nepal. BMC Pediatrics, 18(1). https://doi.org/10.1186/s12887-018-1176-x
- Popescu, C. R., Cavanagh, M. M., Tembo, B., Chiume, M., Lufesi, N., Goldfarb, D. M., Kissoon, N., & Lavoie, P. M. (2020). Neonatal sepsis in low-income countries: epidemiology, diagnosis and prevention. Expert Review of Anti-infective Therapy, 18(5), 443–452. https://doi.org/10.1080/14787210.2020.1732818
- Rafi, M. A., Miah, M. M. Z., Wadood, A., & Hossain, M. G. (2020). Risk factors and etiology of neonatal sepsis after hospital delivery: A case-control study in a tertiary care hospital of Rajshahi, Bangladesh. PLOS ONE, 15(11), e0242275. https://doi.org/10.1371/journal.pone.0242275

- Risk factors in early neonatal sepsis. (2006, June 1). PubMed. https://pubmed.ncbi.nlm.nih.gov/18603896/
- Salah, A., Al-Subol, I. H., Hudna, A. S., Alhaj, A., Alqubaty, A. R., Farie, W., Sulieman, D., Alnadhari, O., Alwajeeh, T., Alobathani, F., Almikhlafy, A. A., & Mahdy, M. a. K. (2021). Neonatal sepsis in Sana'a city, Yemen: a predominance of Burkholderia cepacia. BMC Infectious Diseases, 21(1). https://doi.org/10.1186/s12879-021-06808-y
- Salsabila, K., Toha, N. M. A., Rundjan, L., Pattanittum, P., Sirikarn, P., Rohsiswatmo, R., Wandita, S., Hakimi, M., Lumbiganon, P., Green, S., & Turner, T. (2022). Early-onset neonatal sepsis and antibiotic use in Indonesia: a descriptive, cross-sectional study. BMC Public Health, 22(1). https://doi.org/10.1186/s12889-022-13343-1
- Sands, K., Carvalho, M. J., Portal, E., Thomson, K., Dyer, C., Akpulu, C., Andrews, R., De Oliveira Ferreira, A. C. A., Gillespie, D., Hender, T., Hood, K., Mathias, J., Milton, R., Nieto, M., Taiyari, K., Chan, G. J., Bekele, D., Solomon, S., Basu, S., . . . Walsh, T. R. (2021a). Characterization of antimicrobial-resistant Gram-negative bacteria that cause neonatal sepsis in seven low- and middle-income countries. Nature Microbiology, 6(4), 512–523. https://doi.org/10.1038/s41564-021-00870-7
- Schlapbach, L. J., Van Rossum, A. M. C., & Carrol, E. D. (2021). Antibiotics for neonatal sepsis in low-income and middle-income countries—where to go from here? Lancet Infectious Diseases, 21(12), 1617–1618. https://doi.org/10.1016/s1473-3099(21)00199-7
- Sehgal, R., Gaind, R., Chellani, H., & Agarwal, P. (2007). Extended-spectrum β lactamase-producing gram-negative bacteria: clinical profile and outcome in a neonatal intensive care unit. Annals of Tropical Paediatrics, 27(1), 45–54. https://doi.org/10.1179/146532807x170501
- Sulikah, S. R. O., Hasanah, M., Setyarini, W., Parathon, H., Kitagawa, K., Nakanishi, N., Nomoto, R., Osawa, K., Kinoshita, S., Hirai, I., Shirakawa, T., & Kuntaman, K. (2022). Occurrence of Carriage of Multidrug Resistant

Enterobacteriaceae among Pregnant Women in the Primary Health Center and Hospital Setting in Surabaya, Indonesia. Microbial Drug Resistance, 28(1), 48–55. https://doi.org/10.1089/mdr.2020.0506

- Toan, N. D., Darton, T. C., Huong, N. H. T., Nhat, L. T. H., Nguyen, T. N. T., Tuyen, H. T., Thinh, L. Q., Mau, N. K., Tam, P. T. T., Phuong, C. N., Thành, N. L., Minh, N. N. Q., Xuan, N. M., Thuong, T. C., Hưng, N. T., Boinett, C. J., Reece, S. T., Karkey, A., Day, J., & Baker, S. (2022). Clinical and laboratory factors associated with neonatal sepsis mortality at a major Vietnamese children's hospital. PLOS Global Public Health, 2(9), e0000875. https://doi.org/10.1371/journal.pgph.0000875
- Vatne, A., Klingenberg, C., Rettedal, S., & Øymar, K. (2021). Early-Onset Sepsis in Neonates - A Population-Based Study in South-West Norway From 1996 to 2018. Frontiers in Pediatrics, 9. https://doi.org/10.3389/fped.2021.634798
- Wu, J., Chen, C., Tsao, P., Hsieh, W., & Chou, H. (2009). Neonatal sepsis: A 6-Year analysis in a neonatal care unit in Taiwan. Pediatrics and Neonatology, 50(3), 88–95. https://doi.org/10.1016/s1875-9572(09)60042-5
- Zaidi, A. K. M., Awasthi, S., & De'Silva, H. (2004). Burden of infectious diseases in South Asia. BMJ, 328(7443), 811–815. https://doi.org/10.1136/bmj.328.7443.811
- Zaidi, A. K. M., Ganatra, H. A., Syed, S., Cousens, S., Lee, A. C. C., Black, R. E., Bhutta, Z. A., & Lawn, J. E. (2011). Effect of case management on neonatal mortality due to sepsis and pneumonia. BMC Public Health, 11(Suppl 3), S13. https://doi.org/10.1186/1471-2458-11-s3-s13