# CHARACTERIZATION AND ANTIBIOTIC RESISTANCE OF GRAM NEGATIVE BACTERIA INVOLVED IN SEPSIS AMONG UNDER FIVE CHILDREN IN AKWA IBOM STATE NIGERIA

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## ABSTRACT

Sepsis is a systematic illness in which bacteria enter a normal sterile place in the body. Antimicrobial resistance complicates sepsis management across all settings, particularly in high-risk populations such as newborns and patients in intensive care units. In other words, while sepsis affects individuals of any sex and of any age, there are significant disparities in the burden of disease. Sepsis disproportionately affects vulnerable population such as pregnant women, newborns, young children, older persons, individuals with underlying chronic conditions and the immune-compromised. . In this review, we have discussed the Resistance of Gram-Negative Bacteria involves in Sepsis among under five Children, the recent challenges, and possible areas for future research considerations.

**Keywords:** Sepsis, Antibiotic, Resistance, Gram-Negative Bacteria, Children.

## Introduction

Sepsis, a syndrome of physiologic, pathologic, and biochemical abnormalities induced by infection, is a major public health concern accounting for more than 2.5 million global annual newborn deaths and children under 5 years of age (Rudd *et al*., 2020). According to WHO, 2020 on global report, sepsis mortality is often related to suboptimal quality care, inadequate health infrastructure, poor infection prevention measures place, late diagnose, and inappropriate clinical management. The most susceptible age group of sepsis is children and more importantly new born and young infants. It also strikes aged people in more tendencies (Raheema and Qaddoori, 2021). A report by Dhir *et al.,* 2021 on sepsis showed the rate of fatality which was significantly high in children under the age of 5. However, sepsis among children involves neonate [new born or infant younger than 90 days (3 months old; early and late onset sepsis)] and those above 3 months. Early onset sepsis is sepsis in new born at or before 72 hours after birth and is generally caused by the transmission of pathogens from the female genitourinary system to the fetus thereby exposing the new born to infection during delivery (Wynn, 2016). Late onset sepsis is sepsis in new born that occurs after the delivery of a new born usually 3 to 4 days after birth (Wynn, 2016). It is caused by pathogens that enter from environment such as contact from health care workers. It may also be caused by a late manifestation of vertically transmitted infection; infants that require intravascular catheter insertion, or other invasive procedure that disrupt the mucosa are seen to be at risk of developing late onset sepsis (Ershad *et al*., 2019).

In childhood, sepsis accounts for 60-80% of lost lives, with more than 6 million new born and children affected by sepsis annually (Reinhart *et al*., 2013). However, liu *et al*., 2015 also in 2013 estimated 6.3 million live born children worldwide who died before the age of 5 years. Among them, nearly half (51.8 %) died of infections with sepsis accounting for 15 % of overall under 5-year infection related childhood deaths. Sepsis is known to be responsible for >100,000 cases of maternal sepsis each year, and in some countries, it has become a greater threat in pregnancy than bleeding (Garrod *et al*., 2011). Countries with high income earnings is suffering from sepsis at an annual rate 8-13 % (Hall *et al*., 2011), reason includes; the aging population, increasing use of high-risk interventions in all age groups, drug resistant development and varieties of pathogens. In developing world, malnutrition, poverty and lack of access of vaccines contribute to death. According to Wen *et al*., 2012, Nigeria is the second highest contributor to under 5 mortalities (much due to sepsis) in the world. However, in 2017, children accounted for half of all sepsis cases worldwide, with an estimated 20 million cases and 2.9 million fatalities in under 5 years children. An estimated 17 million of these cases and 3.5 million of the deaths occurs in Africa

(Rudd *et al*., 2020; Keeley and Nsutebu 2021). Sepsis also accounts for 15 % of new born death and is the most common cause of death in infants globally. According to the world health organization, sepsis due to severe pneumonia, severe diarrhea, severe malaria and severe measles are responsible for the highest deaths in children (Weiss *et al*., 2015).

Sepsis is one of the most common causes of children's hospitalization and is estimated to cause 20 % of all new born deaths worldwide (Peterside *et al*., 2015). A study between September 2018 and November 2019 on assessing predictor's mortality among children with sepsis at health facility in North western Nigeria was carried out by Hassan-Hanga *et al*., 2022. A total of 326 children were recruited, with median age 2 years, about 54.0 % of the children were boys, and 53.1 % were within 1-5 years age group. *Salmonella typhi* (5.7 %), *Klebsiella pneumoniae* (2.3 %) and *Staphylococcus aureus* (2.0 %) were the predominant organisms cultured from blood of the children. It was observed that case fatality rate was higher in children <1 year (13.6 %) amongst the total death recorded with case fatality rate of 10.7 %. A related study in Nigerian hospital at special care baby unit was carried out by Ogundare *et al*., 2019. Children with sepsis were responsible for 16 % of special care baby unit admissions. Among the 72 babies with sepsis, 56 (77.8 %) had early onset sepsis compared to 16 (22.2 %) of late onset sepsis. Low birth weight (p=0.01) and perinatal asphyxia (p=0.01) were significantly associated with early onset sepsis, while for late onset sepsis, delivery outside the health facility (p=0.01) was the only significant risk factor. Out *et al*., 2015 reported the mobility and mortality of children admitted within 2015 to 2016, in a special care baby unit in federal medical Centre Birnin kudu Jigawa state, Nigeria. A total of 205 children were admitted, with the ratio of males to females 2:1. The results showed that children (new born) sepsis (32.2 %), with birth asphyxia (29.3 %) and prematurity (18.5 %) was the major cause of mobility. Adedokun and co-workers also reported a retro specific evaluation to determine organisms present in early and late onset of new born with sepsis in university of Port Harcourt teaching hospital (UPTH) Nigeria between January to December 2007. The results showed that Klebsiella *spp* was the most common pathogens accounting for 37.8 % of the total isolates. *Staphylococcus aureus* (28.4 %), *Escherichia coli* (11.8 %), unclassified coliforms (8.3 %), *pseudomonas spp* (4.9 %), *Enterococcus spp* (2.9 %), *Coagulate-negative staphylococcus* (2.5 %) and *Proteus spp* (3.4 %) (Adedokun *et al*., 2020).

A study between 2011 to 2013 was carried out on causative organisms of new born sepsis in Niger Delta University Teaching Hospital (NDUTH) Bayelsa State by Peterside *et al*., 2015, 233 (46.6 %) of 450 new born admitted in the hospital were screen for sepsis. 97 (43.5 %) of them were blood culture positive, 52 (53.6 %) of isolated organisms were Gram positive and 45 (46.4 %) Gram negative. The most occurrence organisms were *Staphylococcus aureus* (51.5 %), *Escherichia coli* (16.5 %) and *Klebsiella pneumonia* (14.4 %). It was observed that all the isolated organisms showed highest sensitivity to quinolones (an antibiotic derived from quinolone used mostly against Gram negative organisms). Additionally, Ogunkunle *et al*., 2022, discovered *Staphylococcus aureus* with 41.4 % as the leading cause of childhood sepsis which was most sensitive to ampicillin-sulbactam 89 %.

**Classification of Sepsis**

Sepsis is a systematic illness in which bacteria enter a normal sterile place in the body. This definition is said to have taken evidence of systemic inflammatory response syndrome (SIRS) and incorporate it with suspicion of microbial origin. When these criteria include acute organ failure, it is said to be severe sepsis (Weiss *et al*., 2020). Experience in significant drop of blood pressure that can lead to respiratory or heart failure, stroke, failure of other organs and dead (Digiacinto and Johnson, 2021) or Further dysfunction accompanied with refractory hypotension or hypo perfusion while fluid resuscitation is being attempted (Shankar-Hari et *al*., 2016; Weiss *et al*., 2020), is classified as septic shock. However, when organ dysfunction progress to the point that the patient is unable to maintain homeostasis without intervention, it is called multi-organ dysfunction syndrome (MODS) (Plunkett and Tong, 2015).

| Classification | Parameters |
|---|---|
| Systemic inflammatory response | Core body temperature >38 ºC or <36 ºC<br>Heart rate HR ≥ 90 bpm respirations ≥ 20/min<br>(or $PaCO_2$ < 32 mmHg)<br>WBC ≥ 12, 000/µL or ≤ 4000/ µL<br>or >10 % immature. |
| Sepsis | At least two SIRS criteria caused by known or suspected infection. |

| | |
|---|---|
| Severe sepsis | Sepsis with acute organ dysfunction. |
| Septic shock | Sepsis with persistent or refractory hypotension or issue hypoperfusion despite adequate fluid resuscitation. |
| Multi organ dysfunction syndrome | The presence of organ dysfunction in an acutely ill patient such that homeostasis cannot be maintained without intervention. |

(Plunkett and Tong, 2015; Ogbara *et al*. 2021).

In children, sepsis is classified base on the timing of the infection, according to whether the infection was contracted during birth (early-onset) or after birth (late-onset) (Kelvin, 2023). Low birth weight and premature babies are more susceptible to late-onset sepsis because their immune systems are immature. While symptoms can be delicate and nonspecific, some signs include: listlessness, not breastfeeding/feeding well, low body temperature, apnea (gaps in breathing), fever, pale colour, poor skin circulation with cool extremities, abdominal swelling, vomiting, diarrhoea, seizures, jitteriness, yellowing of the skin and whites of the eyes (jaundice) (Kelvin, 2023). Traditionally, sepsis has been classified into community-onset and hospital-acquired (i.e. nosocomial) infection, depending on the place of the infection's gaining (ATSIDA, 2005). This two differ in terms of the host characteristics (e.g. demographics, risk profile, resistance patterns), pathogens and outcomes (Wang *et al*., 2015). For instance, in their study, Hoenigl and colleagues observed a significantly higher 30-day (20.75 vs. 11.20 %, p = 0 · 001) and 90-day (26.83 vs. 12.63 %, p < 0 · 001) mortality rates in people with hospital-acquired vs. community-onset infection (Hoenigl *et al*., 2014) introduced a new category of healthcare-associated sepsis due to an increasing number of sepsis cases associated with outpatient treatment that takes place in communities (e.g. nursing homes, dialysis, long-term home care Facilities. According to the definition of healthcare-associated sepsis, the patient had to have received a medical care in the community/outpatient setting (e.g. intravenous therapy, wound care) 30 days before the bloodstream infection, hospitalization in acute care hospital 90 days before the bloodstream infection, attendance of hospital or haemodialysis clinic, or residence in a nursing home or a long-term care facility (Friedman *et al*., 2002). Although nosocomial and healthcare-associated sepsis are related with respect to source of infection, type of pathogens, susceptibility and the outcome, emerging empirical evidence has shown them to be two distinct entities. Thus, community-onset sepsis has been further divided into healthcare-associated and community-acquired sepsis (Cardoso *et al*., 2014; Hoenigl *et al*., 2014). Baharoon *et al*., 2015 carried out a retrospective evaluation on community versus hospital-acquired severe sepsis and septic shock in intensive care unit. Of the 96 patients, 60 % of cases were due to hospital-acquired infections and 40% were community-acquired. In other words, community and hospital-acquired severe sepsis and septic shock have high mortality rates, 47.2% and 63%, respectively. Guo-Yun *et al*., (2022) reported a retrospective study on community-acquired and hospital-acquired septic shock in children. The patients were followed up until 28 days after shock. Among 298 children enrolled, 65.9% ($n$ = 91) of hospital-acquired septic shock (HASS) patients had haematologic/oncologic diseases, mainly with Gram-negative bacterial bloodstream infections (47.3%). Moreover, 67.7% ($n$ = 207) of community-acquired septic shock (CASS) patients had no clear underlying disease, and most experienced Gram-positive bacterial infections (30.9%) of the respiratory or central nervous system. The 28-day mortality was 62.6% and 32.7% in the HASS and CASS groups, respectively ($P < 0.001$). Platelet [odds ratio (OR) = 0.996, 95% confidence interval (CI) = 0.992–1.000, $P = 0.028$], positive pathogen detection (OR = 3.557, 95% CI = 1.307–9.684, $P = 0.013$), and multiple organ dysfunction syndrome (OR = 10.953, 95% CI = 1.974–60.775, $P = 0.006$) were risk factors for 28-day mortality in HASS patients. Lactate (OR = 1.104, 95% CI = 1.022–1.192, $P = 0.012$) and mechanical ventilation (OR = 8.114, 95% CI = 1.806–36.465, $P = 0.006$) were risk factors for 28-day mortality in patients with CASS. In conclusion, they discovered a distinction between HASS and CASS pediatrics patient with septic shock.

**Bacteria involves in Sepsis (Gram-positive and Gram-negative)**

Bacteria sepsis is said to be the major cause of fatality worldwide. Both Gram negative and Gram-positive bacteria play a major role in causing sepsis. These bacteria produce a range of virulence factors that aid them escape the immune defenses and disperse to remote organs and toxins that interact with host cells through specific receptors on the cell surface and release or activate a dysregulated immune response (Ramachandran, 2014). According to Odetola *et al*., 2007; Stormorken and Powel, 2011, delay recognition of blood stream bacteria increases the risk of mobididity and mortality as they progress to

sepsis, severe sepsis, septic shock and multiple organ dysfunction syndromes. Gao *et al*., (2019), in their report showed organisms causing sepsis in children.

Gram-Negative Bacteria: *Klebsiella pneumonia*, *Escherichia coli*, *Acinetobacter baumannii*, *Enterobacter cloacae, Serratia marcescens, Enterobacter aerogenes, Ochrobactum anthropic, Stenotrophomonas maltophilia, Achromobacter xylosoxidans*, *Chryseobacterium meningosepticum*, *Pseudomonas aeruginosa and Proteus mirabilis* (Sisay *et al*., 2019).

Gram-Positive Bacteria: *Group B streptococcus, Staphylococcus aureus, Coagulase-negative Staphylococcus, Enterococcus faecalis, Enterococcus faecium, Streptococcus mitis, Streptococcus pasteurianus, Streptococcus gallolyticus, Streptococcus milleri*. *Enterobacter species* are motile aerobic gram-negative bacilli belonging to *Enterobacteriaceae* family. The *Enterobacter cloacae* complex (ECC) includes different pathogens, capable of producing a wide variety of infections. The most frequent of it, are *Enterobacter cloacae* and *Enterobacter aerogenes* (Davin-Regli, 2015). In 2019, *E. aerogenes* was reclassified as *Klebsiella aerogenes* due to its high genotypic similarity with the genus *Klebsiella* (Alvarez-Marin *et al*., 2021).

Amongst the organisms above, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus epidermidis*, *Enterobacter cloacae*, *Streptococcus pneumoniae*, *Enterococcus faecium*, and *Acinetobacter baumannii* are the 10 most prevalent species, (Diekema *et al*., 2019). In 2005 *E. coli* replaced *S. aureus* as the most prevalent bloodstream pathogen and *A. baumannii* entered the top 10. *K. pneumoniae* is consistently the third most prevalent bloodstream pathogen, and *P. aeruginosa* has emerged as fourth in prevalence, emphasizing the significance of Gram-negative species in these infections. This small subset of Gram-negative species significantly contributes to disease burden. *E. coli* accounts for 6 to 27% of bacteraemia cases, *K. pneumoniae* for 5 to 13%, *P. aeruginosa* for 4 to 9%, and *A. baumannii* for 1 to 13% (Magill *et al*., 2014).

Recently, Godfrey *et al*., (2022) and Oyekale *et al*., (2022) showed *K.* pneumoniae, *E. coli*, *P. aeruginosa* as the most predominant Gram-negative bacteraemia. Godfrey *et al*., 2022 carried out a study on Aetiology antimicrobial susceptibility and outcome of children with sepsis, there was predominance of male participants (67.5%) with a median age of 2 years and an interquartile range of 10 months to 4 years. Culture positive sepsis was detected among 29.8% of the participants and the common Gram-positive bacteria isolates used were *Staphylococcus aureus* (39.7%), *Coagulase negative Staphylococcus* (35.6%) and Gram-negative isolates were *Escherichia coli* (12.3 %), *Klebsiella spp*. (6.8%) and *Pseudomonas aeruginosa* (5.5%). Shobowale *et al*., (2017) also reported bacteria isolates rates from 100 new born babies to be 34%, which the predominant pathogens were *Coagulase-negative Staphylococci*, *Staphylococcus aureus* and *Klebsiella pneumoniae*. Oyekale *et al*., 2022, in their study showed gram-negative bacteria (67.6%) to be the most predominant isolates of which *Escherichia coli* (29.4%) was the most commonly isolated specie. *Staphylococcus aureus* (23.5%) and *Coagulase-negative Staphylococci* (CoNS 8.8%) were the only Gram-positive bacteria isolated. Similar findings have been reported where Gram-negative bacteria were the predominant isolates from cases of blood stream infections (Gupta and Kashyap 2016; Lee *et al*., 2007). However, some studies have also reported *Staphylococcus aureus* as the most commonly isolated bacterial pathogen from cases of blood stream infections (Mia and Zerin, 2020; Sangita *et al*., 2019). Generally, there is wide variability in the pathogens isolated from cases of blood stream infections in different settings. Gram-positive bacteria were the most common cause of sepsis prior to the advent of antibiotics in the 1950s, but Gram-negative organism became the most predominant after the introduction of antibiotics from the 1960s to 1980. However, from the 1980, Gram-positive bacteria, most commonly *Staphylococcus spp* were thought to cause more than 50% of cases of sepsis (Polat *et al*., 2017). According to Oyekale *et al*., 2022, there is a higher chance of hospital-selected Gram-negative bacteria causing blood stream infections.

Several studies have reported Gram-negative organism (GNO) to be responsible for many deaths in children with sepsis (Jean *et al*., 2012; Carroll *et al*., 2016; Ogbolu *et al*., 2019; Georgios *et al*., 2019; Sisay *et al*., 2019; Breijyeh *et al*., 2020; Olowo-Okere *et al*., 2020; Chelkebe *et al*., 2021; Tessema *et al*., 2021). However, among Gram-negative bacteria, *Escherichia coli, Klebsiella species* and *Pseudomonas aeruginosa* are the most common blood stream isolates (Marchetti and Calandra, 2015). According to Joshi *et al*., (2000) studies, Gram negative organism was seen to be responsible for 67.2% of the cases. *Pseudomonas aeruginosa* was the most common organism (38.3%), followed by *Klebsiella*

*spp*. (30.4%) and *Escherichia coli* (15.6%). Similar pattern has also been reported in Trinidad Orrett, Shurland and Nigeria, Ako-Nai *et al.,* (1999) with *Pseudomonas aeruginosa* contributing 26%, *Klebsiella pneumonia* 14%, *Escherichia coli* 12% and *Enterobacter aerogene* 5%. However, study from Bangladesh revealed that Gram negative organism was responsible for almost 73% of episodes of new born babies with sepsis, showing *Escherichia coli* as the most common cause (30%) followed by *Klebsiella spp*. (23%) (Ahmed *et al*. 2002).

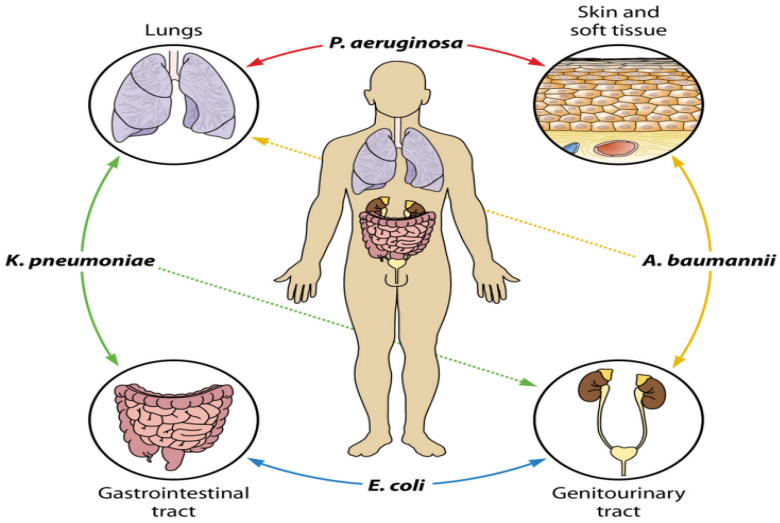


**Figure 1:** Gram negative species are adapted to colonize or infect diverse initial sites, which may progress to secondary bacteraemia.

Gram negative bacteraemia is also involved with intermittent bacterial presence in the blood (Canzoneri *et al*., 2017), that arises often, as a secondary infection germinating from an initial source which moves into the blood stream. In these bacteria, there is virulence factors needed for initial site invasion. Pathogens have to employ an array of factors known as virulence factors that protect them from the host innate immune system and enable them to cross mucosal barriers, disseminate and replicate in distant organs (Bergsten *et al*., 2004; Merrell and Falkow, 2004). Importantly, each stage of infection involves the expression of different virulence factors depending on the stage of infection. Some of the most important bacterial virulence factors are toxins; endotoxin or lipopolysaccharide (LPS) that is present in the outer membrane of the Gram negative bacterium and many other secreted exotoxins and enterotoxins in other bacteria. Holmes and co-worker showed the three phases in Gram negative bacteraemia pathogenesis.

Step 1: Invasion: Bacteria invade initial sites of colonization or infection and evade host immune responses using mechanisms such as capsule production (*K. pneumoniae*) and secretion of exotoxins (*P. aeruginosa*). Initial-site specificity varies by species, with certain bacteria being adapted for invasion at specific sites.

Step 2: Dissemination: After invasion, bacteria over ride host barriers, such as immune response (epithelial) and spread from initial body sites to the blood stream. Dissemination requires factors such as adhesins and exotoxins (*P. aeruginosa*) or activation of specific pathways in epithelial cells (HIF-1α for *K. pneumoniae*).

Step 3: Survival: Bacteria adapt to survive in the blood and blood filtering organs, that is, once in the blood, species must survive a new environment through metabolic flexibility (*C. freundii* and *S. marcescens*) and evade immune clearance with capsule production. Each bacteraemia phase must be investigated to better comprehend pathogenesis at both species-specific and multi-species levels (Holmes *et al*., 2021).

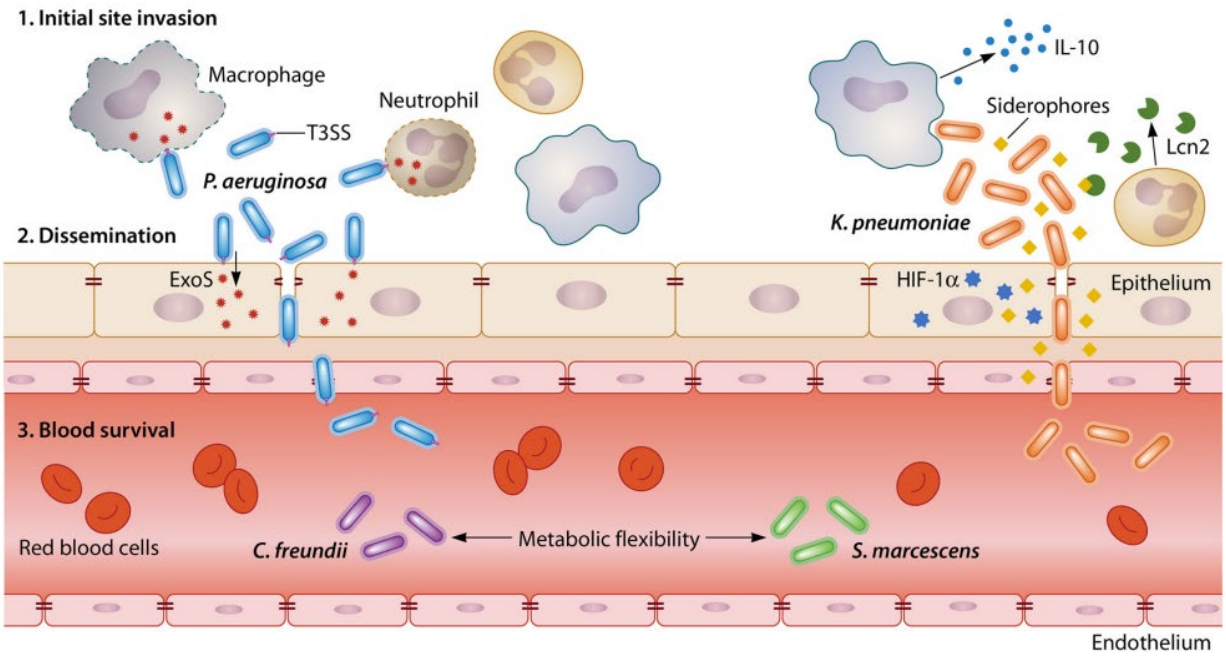


**Figure 2:** Gram Negative Bacteraemia Pathogenesis

**Signs and Symptoms of Sepsis**

Sepsis symptoms can range from mild to severe. According to Gauer, (2013) common generalized symptoms of sepsis include: Fever, chills; rigors may be reported, confusion, anxiety, fatique, malaise, myalgia, dyspnea, nausea, vomiting and decreased urination.

According to Gauer, (2013) localizing symptoms may include:

- Headache and stiff neck when meningitis, is the cause of sepsis.
- Cough and pleuritic chest pain with pneumonia.
- Abdominal pain with gastrointestinal or genitourinary source.
- Diarrhoea in gastrointestinal luminal infections such as *Clostridioides difficile* or toxigenic *Escherichia coli* infection.
- Flank pain and dysuria with kidney infection.
- Bone or joint pain with osteomyelitis or septic arthritis.
- Skin or soft tissue pain with abscesses, wounds or other soft tissue infections.
- Elderly person may have limited or non-specific symptoms (example, poor oral intake inanition).

**Table 1: Signs and Symptoms that should Prompt Quick Clinical Assessment for Sepsis in Children**.

| | |
|---|---|
| Fever>38°C | Hypothermia |
| Tachypnoea | Apnoea |
| Difficulty in breathing/ respiratory distress | Cyanotic/mottled skin/ashen appearance |
| Tachycardia | Bradycardia |
| Abnormal capillary refill time (> 3seconds) | Reduced urine output |
| Weak pulses | non-blanching rash |
| Altered mental status (irritability, inappropriate crying, confused) | Inappropriate drowsiness (difficult to arouse, lethargic or obtunded) |

(NICE, 2016).

Goldstein *et al*., (2005), states, sepsis varies depending on the age of a child, neonates and infants usually shows non-specific signs and symptoms and older children often shows features of a systematic inflammatory response syndrome. Thus, clinicians should have a high catalogue of distrust when reviewing a child with non-specific features, as it may be the early presentation of sepsis (Lambert *et al*., 2017; Parshuram *et al*., 2011). Pediatric Early Warning Scores (PEWS) in both the emergency department as well as for patients admitted to the ward is recently used in a large number of health care systems; this may help to recover early identification of the demoralizing children (Lambert *et al*., 2017; Parshuram *et al*., 2011).

**Complications of Sepsis**

Complications are more likely in severe cases and it can be fatal. Bauer *et al*., (2020), found that the mortality rate for sepsis after 90 days was 32.2 %, as well as mortality rate for septic shock after 90 days, 38.5% and 30% to 40% (Mayo Clinic, 2023). These complications include;

- Blood clots.
- An increased risk of infection.
- Tissue death (gangrene), requiring amputation of affected limb, toes or finger.
- Organ failure, particularly the brain, kidneys, heart, and lungs.
- Disseminated intravascular coagulopathy (Mayo Clinic, 2023; Kelvin, 2023).

**Risk Factors of Sepsis**

Risk factor associated with sepsis and severe sepsis is numerous and most of these factors are in relation with the ability of a patient to fight infection and the probability that acute organ failure develops in response to infection. Generally, greater risk is associated with male gender, age, black race and chronic health condition. Age is considered the most important risk factor and as patients age, the occurrence of severe sepsis is said to increase largely such that a patients of 65 years old could account for more than 50% of severe sepsis cases (Mayr *et al*., 2014). In other words, new born babies acquire a high occurrence of severe sepsis and septic shock as well compared to the total population. Globally, there is an estimation of over 36% mortality rates of all new born babies (Dellinger *et al*., 2013). According to Shane and Stoll, 2014, immature immune systems and early exposure to several microbial agents, including those stemming from maternal source, have made sepsis in children very dangerous with the case fatality rate ranging from 7% to 25%. In their study also, group B *Staphylococcal* and to a lesser degree *E. coli*, infections appear to be among the majority cases with early onset, coagulase negative *Staphylococcus* species and *Staphylococcus aureus* for late onset sepsis. More than half of patients with severe sepsis have at least one chronic health condition simultaneously. The most common chronic conditions are immune insufficiently (primary or secondary), cancer, chronic obstructive pulmonary disease, chronic renal disease, diabetes and chronic liver disease (Shane and Stoll, 2014). Situational risk factors include: immunosuppressive drugs, malnutrition, prosthetic devices and residence in long term care facilities. In addition, an environmental factor such as cold weather is in accordance with greater incident of severe sepsis and increased mortality despite a similar severity of illness (Mayr *et al*., 2014).

Ogundare *et al*., (2016), in a study in Nigerian Hospital, highlighted unsupervised delivery (delivery outside the health facility p= 0.01) with birth asphyxia (p= 0.01) and low birth weight (p= 0.01) as some risk factors associated with sepsis, which is in line with a study by Shobowale *et al*., (2017). Another study by Olorukooba *et al*., 2020 in North West Nigeria revealed premature rupture of membrane PROM and urinary tract infection UTI during pregnancy as the risk factors for new born with sepsis. Their result was said to be consistent with the findings in Soweto by Utomo, (2010); Adatara *et al*., (2019), on risk factors of new born with sepsis. According to Endale *et al*., (2016), early rupture of membrane and prolonged labour increases the chance of ascending microorganisms from birth canal into the amniotic sac and foetal compromise as well as asphyxia which frequently leads to sepsis. However, new born babies born to mothers with UTI during pregnancy are said to be two times more likely to develop sepsis (Olorukooba *et al*., 2020). UTI is often associated early-onset sepsis and if untreated during the third-trimester pregnancy or labour, may lead to colonization of the birth canal by the infectious agent (Akindolire *et al*., 2016). Ogbara *et al.,* (2021), in their report on factors that may contribute to new born with sepsis in Jos university teaching hospital, Nigeria observed that delivery at home is risky with the highest percentage of culture proven sepsis (52.2 %). They also observed that mothers with no formal education and those with only primary education had high proportions of culture proven sepsis (41.1% and 58.8% respectively), which is in accordance with a study by Onyedibe *et al*., (2012). Shobowale *et al*., (2016), reported some risk factors for sepsis from Lagos state university hospital, Nigeria: patients born outside a tertiary hospital were more at risk with p= 0.15 and a change in antibiotic therapy. Those who had any change in antimicrobials were less likely to acquire sepsis (p= 0.0001). Also, babies who had instrument-assisted delivery were 3 times more likely to have late-onset sepsis with risk factor p=0.02, compared to other new born with suspected sepsis. Lack of antenatal care and poor breast feeding has also been highlighted by John *et al*., (2015), as risk factors of sepsis.

Bech *et al.,* (2022), identified multiple risk factors of sepsis in 10 different sub-saharan African countries, which Nigeria is one of the major countries. The risk factors were classified as neonatal, maternal or sociodemographic. Neonatal risk factor: resuscitation at birth, birth weight (1.5 kg-2.5 kg), low Apgar score at the first and fifth minute, pre-maturity (< 37 weeks), no crying after birth, male sex. Maternal: prolonged labour, premature rupture of membrane (PROM), multiple digital virginal examinations, meconium-strained amniotic fluid, intrapartum fever, foul-smelling vaginal discharge. A study in Ethiopia by Birrie *et al*., (2022), on associated factors among new born with sepsis identified maternal PROM and UTI as risk factors for new born with sepsis and children who receive resuscitation at birth. This study is consistent with Agnche *et al*., (2020), in Jamma; Bayana *et al*., (2020), in Mekelle; and Gebremedhin *et al*., (2016), in Gondar. Another study from Zambia by Kabwe *et al*., (2016), showed a reduced risk of new born with sepsis born to HIV positive mothers to be [odds ratio, 0.46 (0.23-0.93); p= 0.029]. other researchers also highlighted risk factors in their studies; catheter used (47%) and prolonged stay (38%), Oliva *et al*., (2021); age of onset, APGAR Score, birth weight and length of hospital stay (Leal *et al*., 2012).

**Antibiotic Resistance of Gram Negative Bacteria**

Globally, antibiotic resistance is a serious public health issue (WHO, 2018). It is a natural process which occurs when bacteria evolve to resist the medicines that are being used to eradicate them. It is one of the greatest tragedies of the 21st century, which has undermined the progress in health care and others (CDC, 2019). After so many years of saving millions of lives and changing health care practices, there is an emergence of resistance of bacterial pathogens to nearly all antibiotics (Ventola, 2015). Black and co-worker in 2010 showed an estimation of children under 5 years of age worldwide with 6 % of new born and 14 % childhood death caused by bacteria. Successes that have been achieved in various aspects of modern medicine including surgery, cancer chemotherapy and organ transplantation is also under a threat due to the emergence and widespread of antibiotic resistant bacteria (WHO, 2014). Death attributed to antibiotic resistance have been estimated to be more than 700,000 annually and are seen to exceed 10 million by the year 2050, if serious action is not taken (World Bank, 2016).

Emergence of antibiotic resistance is a natural phenomenon in most bacterial species, but their spread is being driven a lot of factors; over use and misuse of antibiotic in health care system (Roca *et al*., 2015), lack of infection control practices, over population, poor sanitation and hygiene (Ayukekbong *et al*., 2017). According to Wang *et al*., (2015), overuse of antibiotics in children is more severe than in adult and since children more often come in contact with pathogens from foods and environment, they are more vulnerable to infections (Tan *et al*., 2022). Poor regulatory system that enables easy accessibility to all antimicrobial agents in most developing countries especially in Africa also contributes to the spread of drug resistant bacteria (Sharma *et al*., 2017; Osei-Safo *et al*., 2016). In other words, resistance among Gram negative bacteria has become the main problem in the world (Ho *et al*., 2010). It has exceeded Gram positive organisms in several reports on blood stream infections in children from African countries (Wen *et al*., 2021; Sand *et al*., 2021; Oliva *et al*., 2021; Mutlu *et al*., 2011; Kenneth *et al*., 2015; Gao *et al*., 2019). Beshah *et al*., (2022), reported antibiotic drug resistance of Gram negative bacteria; from their percentage, a high prevalent of Gram negative bacteria was seen. The highest percentage was found in new born and children. Among the total drug resistant bacteria, 148 (66.67 %) were identified in children below 6 years.

Olowo-Okere *et al*., (2020), in Sokoto, Northwest Nigeria revealed a growing prevalence of Gram negative bacteria resistant to commonly prescribed antibiotics. Their study showed a high multidrug resistant Gram negative bacterial infection to be predominantly caused by *Escherichia coli*, *Klebsiella Pneumoniae* and *P. aeruginosa,* which is in accordance with a study by WHO, 2014; Breijyeh *et al*., 2020. Tessema *et al*., (2021), reported antibiotic resistance pattern of important Gram negative bacteria *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumonia*, *Enterobacter cloacae* from new born babies. *Escherichia coli* showed the highest resistance to ampicillin (73.9 %). Le Doare *et al*., (2015), carried out a review on antibiotic resistance rates among Gram negative bacteria in children with sepsis resource-limited countries. African countries were inclusive, which Nigeria was one of them. In new born, *Klebsiella pneumoniae* median resistance to ampicillin was 94% and Cephalosporins 84% in Asia, 100% and 50% in Africa. It was observed that the specific pathogen resistance overall was *Klebsiella* species with highest level of resistance. In children (3 months to 5 years), pathogen identified was *Salmonella spp*, especially non *typhoidal Salmonella*, were the most Gram negative bacteria reported

in children in Asia. The isolates demonstrated over 32% resistance to ampicillin and 10% resistance to ciprofloxacin (Tsering *et al*., 2011; Holt *et al*., 2010; Schwarz *et al*., 2010). Over one third of isolates (37.3%) were resistance to nalidixic acid (Holt *et al*., 2010; Manchanda *et al*., 2006). However, higher rates were found in African studies (ampicillin 85% and ciprofloxacin 10%, respectively (Schwarz, *et al*., 2010; Vandenberg *et al*., 2010). In addition, resistance of other *Enterobacteriaceae*, including *Escherichia coli* and *Klebsiella* were also reported in African countries. High levels of resistance to ampicillin 58% (0% - 100%), gentamicin 30% (0% - 51.2%) and ceftriaxone 30% (0% - 64%) were seen in *Klebsiella* infection and over 50% resistance rates to ampicillin were noted for *Escherichia coli* isolates (Nwadioha *et al*., 2011; Onipede *et al*., 2009). Martin *et al*., (2017); Oliphant and Eroschenko, (2015), showed in their study a high rate of antibiotic resistance among important Gram negative pathogens, *Escherichia coli*, *K. pneumonia*, *P. aeruginosa*, *P. mirabilis*, *Enterobacter species* and *Acinetobacter species* to have exceeded 50% for penicillin. It was also seen that more than 40% of the strains were resistant to third-generation cephalosporin and aminoglycosides.

Ogbolu *and* co-worker in 2019, reported high-level of antibiotics in Gram negative bacteria from Nigeria. *Escherichia coli* were most commonly resistant to the third generation cephalosporins (93.7%) and carbapanem (59.4%) followed by *Pseudomonas spp*. (91.7%) to third generation cephalosporins and 51.7% to carbapenems. Their study showed a very high prevalence of resistance >50% among Nigerian Gram negative bacteria isolates to three key classes of antibiotic compared to other areas of the world. Olowo-Okere *et al*., (2020), carried out an investigation on the prevalence of multi drug resistant Gram negative bacterial infections among patients in health care facilities, North West Nigeria. Among the 735 randomly selected bacterial isolates, 397(54.0%) were Gram negative bacteria; *Escherichia coli* 104 (26.2%), *Klebsiella spp*. 58(14.6%) were the most common Gram negative pathogens. Chelkebe *et al*., (2021), reported Gram negative bacteria and their antibiotic resistance pattern in patients with wound infection in Ethiopia to be 59% which was compared to findings in Tanzania by Carroll *et al*., (2016), where Gram negative bacteria accounted for 85% of the cases. It was observed that the pooled estimates were *Escherichia coli* (17%), *Klebsiella pneumonia* (11%), *P. aeruginosa* (11%), *P. mirabilis* (8%), *Acinetobacter species* (4%), *Citrobacter species* (4%) and *Enterobacter species* (3%). Another report in Ethiopia by Sisay *et al*., (2019), showed the pooled estimates of *Escherichia coli*, *Klebsiella pneumonia*, *P. aeruginosa* and *P. mirabilis* to be 13%, 9%, 9% and 8% respectively. However, due to the above report, it was observed by the researchers that *E. coli*, *K. pneumonia*, *P. aeruginosa*, *P. mirabilis*, *Citrobacter species*, *Enterobacter species* and *Acinetobacter* were the most prevalent Gram negative pathogens with an alarming rate of resistance to commonly used antibiotics, which is in line with a study by Jean *et al*., (2012); Georgios *et al*., (2019).

**Epidemiology of Sepsis**

Epidemiology revolves around the question of who, where, when, what and how about a disease. It is study of determinants and distribution of disease occurring in human population (Agege *et al*., 2020). The occurrence and prevalence of children with sepsis varies between developed world and developing countries. Many researchers have reported the epidemiology of sepsis in children and new born (Akuirene *et al*., 2020). A study in the United States by Watson *et al*., (2003), on epidemiology of severe sepsis in children showed highest in infants (5.16 per 1000), which fell emphatically in older children with (0.20 per 1000 in 10-14 years old). It was 15% higher in boys than girls (0.60 versus 0.52 per 1000, $p < 0.001$). Hospital mortality was 10.3% (6.2 per 1000 population). Half of the cases had underlying disease (49.0%) and over one fifth (22.9%) were low birth-weight new born, which meant that infants were at highest risk especially those with a low birth weight. Consequently, epidemiologic studies conducted in developing countries on pediatric sepsis showed higher prevalence of pediatric sepsis. Jaramillo-Bustamante *et al*., (2012), observed in Colombia that among the 1,051 children from 1 month to 17 years with sepsis diagnosed within the first 24 hour of pediatric intensive care unit's admission, 25% had severe sepsis and 48% had septic shock. Lower prevalence rates were observed in a single center retrospective study conducted in Paquistan by Khan *et al*., (2012), 17.3% children from 1 to 14% years had sepsis of many severities age. A study by Wang *et al*., (2014), among hospitalized children in China, also found 5.5% sepsis prevalence among 27,836 children admitted to the 11 participating hospital. Out of 1,530 sepsis patients, the authors reported that 7.9% had severe sepsis and 2.1% had septic shock and estimated an incidence of 181 cases per 100,000 children per year. However, Humoodi *et al*., (2021), also reported epidemiology of pediatric sepsis in pediatric intensive care (PICU) unit at

Saudi Arabia. The study was carried out between January 1, 2013 and December 31, 2017. Of the 2389 total admissions to the PICU 113 patients (4.9%) met the definition of septic and 50.4% for septic shock. Most patients (66.3%) were less than 6 years old and 52% were male, 85 patients (75.2%) had underlying comorbidities. The respiratory system was the most common primary site of infection. Bacterial and viral infections were the leading infections with the rates of 29.2 and 21.2% respectively. The median duration of PICU stay was 8 days and the 28 day PICU pre-existing percutaneous central venous catheter were associated with a significant increase in mortality, with adjusted odds ratios of 3.6 (95% confidence interval: 1.30-9.93) and 9.27 (95% confidence interval: 1.28-67.29), their study finally showed a high mortality rates in incidence of sepsis. Epidemiological review on new born with sepsis in Nigeria was carried out by (Ogbara *et al*., 2021). The study showed no decline in the mortality rate of new born with sepsis. In the same vein, Medugu *et al*., 2018 also carried out a systematic review in Nigeria, on new born with sepsis. Out of 24% (2,280) cases selected for review, the incidence of new born was 1.8% live births which ranges from 7-55 per 1000 live births. This was attributed to poor parental education and low-income factors. Within 2015 to 2016, Nwankwor *et al*., (2019), carried out a study to determine the mobility and mortality of new born admission in the special care baby unit in federal medical Centre Birnin Kudu, Jigawa State, Nigeria. A total of 205 new born were admitted, with the ratio of males to female 2:1. The result showed that the major cause of mobility was new born with sepsis (32.2%), birth asphyxia (29.3%) and prematurity (18.5%). The overall mortality rate was 7.16% with birth asphyxia accounting for 13(40.6%) of the total death. Chukwumeze *et al*., (2021), showed an epidemiology of children with severe sepsis in North West Nigeria. The study was between November 1, 2018 and August 31, 2020 with admission of 234 patients with sepsis. Most patients were below the age of 2 years and most were admitted to the pediatric ward. 35% (n=82) of severe sepsis patients died during the hospitalization with almost half (49%) dying with 24 hours of admission to hospital. Most inpatient therapeutic feeding Centre (ITFC) patient (91%) were younger than 2 years of age, which was compared to 64% in the pediatric isolation ward $p< 0.001$. it was observed that ITFC had a significantly higher mortality rate compared to those in the pediatric and isolation ward (49% Versus 28%). However, a total of 1965 patients were evaluated in tertiary hospital Port Harcourt, Nigeria by Onubogu and West, (2022), to know the epidemiology of the diseases causing morbidity and mortality. Of the 1965 children, the ratio of male to female was 1:3:1. Their age ranged from one day old to 16 years old with 57.1% (1131) aged < 2 years. Among the infectious diseases analyzed, 234 children had sepsis (11.9%). It was observed that, children with the first 5 years of life constituted the highest number of patients seen in the children's emergency room with male predominance. Higher prevalence rates of septicaemia in children were reported in other Nigerian studies by Onipede *et al*., (2009), (27%), Meremikwu *et al*., (2005), (48.9 %).

Globally, for both sexes and all age groups combined, the most common underlying cause of sepsis-related death was lower respiratory infection in every year from 1990 to 2017 with 2.8 million (95% uncertainty interval UI, 2.3-3.2). Among children younger than 5 years, the three most common cause of sepsis-related deaths in 2017 were new born disorders [801615 (95% UI 627191-996840) deaths], lower respiratory infections [641682 (508331-748106) deaths] and diarrhoeal diseases [447783 (340224-532225) deaths] with highest number of males than female 164.2 Versus 134.1 (95% UI 150.1-180.1 per 100000 Vs 123.6-146.1 per 100000 respectively (Rudd *et al*., 2020). In other words, global epidemiology of sepsis in children is quiet difficult owing to economic and diagnostic factors. A detailed review on 2019 showed the following results in countries with a high level of economic development, the occurrence of severe sepsis ranged from 1.4% in Japan to 7.7% in the United States. The mortality rate from severe sepsis was 7-17% from septic shock to 51%. In developing countries, the incidence of severe sepsis among children varied from 1% to 25.9%, and the mortality rate was 12.3-34.6%. This was attributed to several diagnostic criteria and economic factors (de Souza and Machado, 2019; Tan *et al*., 2019). Several attempts have been made to estimate worldwide incidence of pediatrics sepsis. In 2014, the original study of the prevalence of sepsis, outcomes and therapies study was published. The study involved 6925 children from 128 intensive care units from North America, Europe, Asia, Australia and New Zealand, South America and Africa. The average occurrence of severe sepsis was 8.2%, but varied from 6.2% in Europe to 23.1% in Africa. However, the mortality rate in all the studied countries was approximately the same amounting to 23-24%. It was observed that majority of patients (77%) were diagnosed with concomitant diseases, which the most common among them were respiratory disorders. The most common focused infection was the respiratory system (40%) and

blood flow (19%) (Dugari and Kisson, 2017; Weiss *et al*., 2015; Plunkett and Tong, 2015; Souza *et al*., 2018). In other words, most cases of sepsis occur before the age of 3 years, which may be as a result of the anatomical and physiological characteristics of young children and children with chronic comorbidities had a higher mortality rate (Prout *et al*., 2018; Ruth *et al*., 2014).

Fleischmann *et al*., (2021), showed an epidemiology study for 2797879 live births and 29608 sepsis cases in 14 countries, most of which were middle-income countries. Random-effects estimates for new born with sepsis in the overall time frame were 2824 (95% Cl 1892 to 4194) cases per 100000 live births, of which an estimated 17.6% (95% Cl 10.3% to 28.6%) died between 2009 - 2018. The incidence was 3930 (95% Cl 1937 to 7812) per 100000 live births based on four studies from low medium income countries. Finally, it was observed that, there was a high rate of mortality in early-onset than late-onset new born with sepsis cases. In 2013, Hartman *et al*., reported the epidemiological studies of the incidence of severe sepsis in children. The study showed an increase in occurrence of severe sepsis (0.56 to 0.89 cases per 1000 children across all age groups). The incidence of severe sepsis was significantly higher in younger age groups (incidence in the neonatal age group and infants aged < 1 year was 9.7 and 2.25 cases per 1000 children compared with 0.23 to 0.52 in children aged 1 to 19 years). It was deduced that severe sepsis was more common in children with comorbidities.

**Laboratory Diagnosis of Sepsis**

The diagnostic criterion for organ dysfunction was modified from the surviving sepsis campaign guidelines to classify patients based on commonly available data in a resource-constrained setting (Mahavanakul *et al*., 2012).

**Table 2: Criteria for Organ Dysfunction in a Resource-Constrained Setting**

| Organ System | Organ Dysfunction Variables |
|---|---|
| Acute Oliguria | Urine output <500 ml per 24 h |
| Azotaemia | Creatinine >177µmmol/L |
| Coagulopathy | Platelets $<100\times10^9$/L |
| Total bilirubin | 34.2 µmol/L or clinical jaundice |
| Respiratory failure | The need for medical ventilation |
| Arterial hypotension | SBP< 90 mmHg or requirement for any vasoactive drugs |

(Dellinger *et al*., 2013).

As recommended, early recognition of sepsis is important because of prompt initiation of therapy likely improves outcomes (Rivers *et al*., 2001). Patients who are admitted already for severe infections should be screened routinely for sepsis using the diagnostic criteria mentioned (Pirozzi *et al*., 2016). In the case of antibiotic administration empirical therapy based on good clinical judgement, is strongly advised while waiting for culture results to guide definitive therapy (Pirozzi *et al*., 2016). However, it has been shown that the optimal time to initiate antibiotic therapy depending on severity of sepsis is within one to six hours of sepsis diagnosis (Rivers *et al*., 2001). According to Isa *et al*., (2013), on diagnosis and treatment of sepsis in North Central Nigeria, antibiotic therapy was all but empirical which was seen to be due to poor yield from blood cultures, delay between clinical diagnosis laboratory results availability. This, often experienced in resource-limited settings leads to high mortality rate in children with sepsis. Moreover, if there is a clinical suspicion of an infection being the etiology of septic shock, there should be no delay in the prompt treatment with antimicrobials. Two or more blood culture should be drawn immediately treatment is about to be initiated and more directed antimicrobials therapy for later on (Dellinger *et al*., 2013). Blood culture should be drawn from peripheral sites, not from existing IV access and there should be a precaution as they are filled properly (>10 ml of blood). If cultures prove to be positive from vascular access sites earlier than peripheral blood site, then vascular access would be the point of entry. In other words, cultures of IV and catheters should be taken with peripheral blood smears to help determine the source of infection. Other useful tools include, Gram stain, which is most common for respiratory tract specimens with positive cultures for lower respiratory tract infections. Concurrently, test such as rapid influenza antigen should be used during proper seasons for additional information. A focused history is a very vital source of information for most diagnosis (Dellinger *et al*., 2013).

According to Dellinger *et al*., (2013), the following should be considered when an infection is suspected (a) General variables

- Fever >38-degree $^0$C
- Hypothermia core temperature <36-degree $^0$C
- Heart rate >90 per min or more than two Standard deviation SD above the normal value range
- Tachypnea
- Altered mental status
- Significant oedema or positive fluid balance >20 mL/kg over/24 hr.
- Hyperglycaemia plasma glucose >140 mg/dL or 7.7 mmol/Lin the absence of diabetes.

(b) Inflammatory variables

- Leukocytosis white blood cell (WBC) >12000/µL
- Leukopenia WBC count < 4000/µL
- Normal WBC count with greater than 10% immature forms (shift or left)
- Plasma C reactive protein more than two above normal value
- Plasma procalcitonin more than two above normal values.

(c) Hemodynamic

- Arterial hypotension systolic blood pressure < 90 mmHg, mean arterial pressure < 70 mmHg or decrease in systolic blood pressure > 40 mmHg in adults less than two SD below normal for age
- Organ dysfunction
- Arterial hypoxemia $PaO_2/FiO_2 < 300$
- Acute oliguria urine output < 0.5 mL/kg/hr for at least 2 hrs despite adequate fluid resuscitation.
- Creatinine increase > 0.5 mg/dL or 44.2 µmol/L
- Coagulation abnormalities INR > 1.5 or a PTT > 60
- Thrombocytopenia platelet count < 100,000/µL
- Hyperbilirubinemia plasma total bilirubin > 4 mg/dL or 70 µmol/L

(d) Tissue perfusion variables

- Hyperlactatemia > 1mmol/L
- Decreased capillary refill or mottling

**Diagnostic Tests for Sepsis; First Tests to Order:**

**Full Blood Count with Differential:** A WBC count ≥15,000 cells/$\mu$L was historically used to identify febrile young children at higher risk of occult bacteraemia (Baraff *et al*., 1993). However, studies conducted in the post-pneumococcal conjugate vaccine era have demonstrated that WBC count has poor test characteristics for bacterial infections across age groups and that no single cut-off value has a sufficient sensitivity or specificity for clinical utility (Stoll and Rubin, 2004; De Williams *et al*., 2014; Mahajan *et al*., 2014; Cruz *et al*., 2017). Abnormal white blood cell count for age (high or low) is one of the diagnostic criteria for systemic inflammatory response syndrome. A low or normal cell count is a feature of the initial phase of illness in severe sepsis and should raise the suspicion of the diagnosis if there are clinical signs that suggest sepsis. Thrombocytopenia (platelet count < 80 000/µL or a decrease by 50% from the highest value in the past three days) in the context of sepsis, is indicative of dispersed intravascular coagulation if related with coagulopathy (Plunkett and Tong, 2015).

**Serum Glucose:** Moderate hypoglycaemia is a blood glucose level of 2.0-3.0 mmol/L and severe hypoglycaemia is a blood glucose level <2.0 mmol/L (Macrae *et al*., 2014). Hyperglycaemia is common as part of the stress response to sepsis. However, hypoglycaemia is not uncommon in young children, due to decreased fluid intake. It can also occur as a side effect of corticosteroid treatment. Hypoglycaemia may also occur as a result of depleted glycogen stores.

**Blood culture:** No single laboratory test will confirm or refute the diagnosis of sepsis, but many can provide supporting or additional useful information (Deep and Duncan, 2020). As many infants and young children with sepsis have a primary bacteraemia, a blood culture is an important investigation (Puopolo *et al*., 2018; Kim *et al*., 2020; Pantell *et al*., 2021). This should be done as soon as possible when sepsis is suspected and ideally before administration of antibiotics; but, empiric antibiotic therapy should not be withheld while awaiting results if sepsis is suspected (Weiss *et al*., 2020). The sensitivity of blood culture is proportional to the volume of blood taken. When using a neonatal aerobic culture bottle in new born, a minimum of 1 mL of blood from venipuncture or freshly inserted vascular catheter

(arterial or venous) is likely to be adequate to diagnose bacteraemia (Polin, 2012; Puopolo *et al*., 2018). When standard aerobic culture bottles are used, a minimum of 4 mL of blood is needed for a valid negative culture at 48 hours. Blood culture results should be reviewed every 12 to 24 hours; most positive results will be detectable within 48 hours and many will be positive within 24 hours (Garcia-Prats *et al*., 2000).

**Urine Analysis and Urine Culture:** Urine analysis (urine sample for nitrites, microscopy, Gram stain and culture) should be considered in all neonates with sepsis (although in the first week of life, a positive result in urine culture may simply reflect a severe bacteraemia). It should be considered in older children with symptoms suggestive of a urinary tract infection. Urine analysis may not be possible until after fluid resuscitation.

**Biomarkers:** Apart from the diagnosis and monitoring of sepsis, biomarkers are also useful for diagnosis and monitoring of the specific organ effects of sepsis. The following laboratory investigations should be requested in children with suspected sepsis:

**Blood Gases:** Although children rarely have arterial blood gases taken in the emergency department, it is often possible to obtain clinically useful information from capillary or venous blood gases.

- A large base deficit is a key marker of severe sepsis and may be the first marker to give a clue to the severity of illness.
- Hypercarbia or hypoxemia is supportive of a diagnosis of respiratory dysfunction (Goldstein *et al*., 2005).
- Hypoxemia: P/F ratio (arterial oxygen pressure/fractional inspired oxygen) < 300 (in absence of cyanotic heart disease or pre-existing pulmonary disease).
- Hypercarbia: Arterial carbon dioxide pressure >65 mm Hg, or 20 mm Hg above baseline level.
- A high fractional inspired oxygen requirement is indicative of sepsis related respiratory failure.
- Pulse oximetry should be ordered as a high requirement for fractional inspired oxygen is indicative of sepsis-related respiratory failure (Goldstein *et al*., 2005).

**Serum Lactate:** Increased serum lactate level is indicative of illness severity in sepsis (Goldstein *et al*., 2005; Garcia-Alvarez *et al*., 2014). It is caused by beta-adrenoreceptor stimulation from endogenous catecholamine up-regulating glycolysis leading to production of a high quantity of pyruvate. This production exceeds the utilization capacity of the tricarboxylic acid cycle and excess pyruvate is converted to lactate. Lactate is often elevated in severe sepsis or septic shock. In certain situations lactatemia may represent decreased oxygen delivery (Garcia-Alvarez *et al*., 2014). Lactate is most reliably assessed using an arterial sample; venous and capillary lactate should be interpreted with caution.

**Serum Electrolytes:** Serum electrolytes are often deranged in sepsis. They should be measured at baseline and regularly until patients improve (Goldstein *et al*., 2005).

Serum Creatinine: Increased serum creatinine (that is, serum creatinine >2 times upper limit of normal or increase in serum creatinine >2 times baseline level) is indicative of sepsis related renal failure (Goldstein *et al*., 2005).

**Liver Function Tests:** Increased bilirubin levels (outside the neonatal age range) or increased alanine aminotransferase is suggestive of sepsis related liver dysfunction (Goldstein *et al*., 2005).

**Coagulation Studies:** In the context of sepsis and thrombocytopenia, abnormal results (international normalized ratio >2; prolonged activated partial thromboplastin time (PTT), decreased fibrinogen level, increased D dimer levels) are indicative of disseminated intravascular dissemination (Goldstein *et al*., 2005; Levi *et al*., 2009).

**C - reactive protein:** Is an acute phase reactant and biomarker used for tracking inflammation in response to infection and tissue injury. Although it is possible to aid in the diagnosis of severe sepsis, CRP is also raised in the following conditions: late pregnancy, active inflammation, bacterial infections, viral infections and elderly age (Clyne and Olshaker, 1999). It is not as specific as serum procalcitonin, but more commonly available. Current practice varies regarding the use of C reactive protein and clinicians should continue to use clinical judgment when diagnosing sepsis. However, C-reactive protein is often integrated into identification of febrile infants with bacterial infections. A C-reactive protein cut-off of 2 mg/dL has moderate sensitivity (88%) and specificity (60%) for identification of febrile children with bacterial infections, with higher levels (e.g, >8mg/dL) having higher specificity (Andreola *et al*., 2007). Other studies have found lower diagnostic utility for C-reactive protein used in isolation to identify septic children (Lamping *et al*., 2018).

**Procalcitonin (PCT):**
Procalcitonin (PCT) has the most favourable test characteristics for the identification of children with bacterial infections, particularly for invasive bacterial infection (IBI) (bacteraemia and/or bacterial meningitis) (Mahajan *et al*., 2014; Trippella *et al*., 2017). Among febrile infants ≤60 days of age, a PCT level of <0.5 ng/mL should be used in combination with other clinical and laboratory parameters to identify infants at low risk of invasive bacterial infection (Gomez *et al*., 2016; Kuppermann *et al*., 2019). For febrile older children, a PCT level of >0.5 ng/mL has low sensitivity (55%) and moderate specificity (85%) for bacterial infections, although its sensitivity is higher for invasive bacterial infection (82%) (Trippella *et al*., 2017). A PCT level of >2 ng/mL has low sensitivity (61%) for IBI but high specificity (94%) and can be used to identify febrile children at higher risk of sepsis (Trippella *et al*., 2017).
**Chest Radiography:** Infants and small children with respiratory distress in the context of suspected sepsis should undergo chest radiography to assess for pneumonic changes (such as lobar consolidation in bronchopneumonia).
**Tests to Consider**
**Lumbar Puncture:** If meningitis with no sepsis is suspected and there is no purpuric or petechial rash, clinicians should consider a lumbar puncture (for cerebrospinal fluid protein and glucose concentrations, microscopy with Gram stain and bacterial culture) to exclude meningitis when the child is stable and can safely undergo the procedure (Polin, 2012). Lumbar puncture is usually contraindicated in children with severe sepsis until the patient is stabilized, as performing a lumbar puncture in severe sepsis may lead to collapse. A positive culture result for cerebrospinal fluid may confirm bacterial meningitis and provide information on the type of pathogen, including sensitivities to antibiotics; protein levels may be increased; glucose levels may be low.
**Meningococcal Polymerase Chain Reaction (PCR) Analysis:** This may help confirm the diagnosis in equivocal or suspected clinical cases of meningococcal sepsis, but not available widely.
**Bronchoalveolar Lavage Culture:** Bronchoalveolar lavage sample for microscopy and culture may be considered for a child in an intensive care unit with a suspected ventilator associated Pneumonia.
**Herpes Simplex Virus PCR (blood and cerebrospinal fluid):** Neonatal herpes simplex infection (either in the central nervous system or disseminated) is infrequent, but an important consideration in children with severe sepsis. Consider ordering if neonatal herpes simplex infection is a possibility. Diagnostic tests to identify sepsis are limited to non-specific biomarkers indicative of a current inflammatory response such as white blood Cell (WBC) count and differential, C - reactive protein (CRP) and procalcitonin (PCT). However, none of these tests are sensitive or specific for diagnosing sepsis and evidence to suggest they exactly predict sepsis is lacking (Downes *et al*., 2020; Cruz *et al*., 2020). According to Lanziotti *et al*., (2016), the cost of PCT test is significantly higher compared with CRP or white cell count. However, there are situations in which a distinctly raised procalcitonin is not predictive, for example, in the setting of moderate to severe acute kidney injury. Based on studies performed in adults, PCT is a good predictive sign that can be used for monitoring therapeutic response and can help guide safe antibiotic de-escalation/ rationalization.
**Prevention and Control of Sepsis**
A good number of sepsis could be prevented through the widespread adoption of practices in good general hygiene and hand washing, cleaner obstetric deliveries, through improvements in sanitation and nutrition, especially among children under 5 years of age, providing clean water in resource poor areas (Kisson *et al*., 2011), and vaccination programs for risk patient populations (Mangia *et al*., 2011). Sepsis mortality can be reduced considerably through the adoption of recognition systems and standardized emergency treatment (Ferrer *et al*., 2008; Levy et *al*., 2010; Barochia *et al*., 2010). According to Reinhart *et al*., 2013, sepsis often diagnosed too late. Patients and health care professionals do not suspect sepsis, and the clinical symptoms and laboratory signs that are currently used for the diagnosis such as raised temperature, increased pulse, breathing rate or white blood cell count are not specific for sepsis. However, lack of reliable systems to aid identification and speed delivery of care creates a low awareness of sepsis among health professionals which also lead to high rate of mortality. The more problematic one is the recognition in new born and children, because the signs and symptoms may not be specific and subtle but reduction is usually fast (Reinhart *et al*., 2013). Moreover, variation in normal physiological parameters with age also contributes to difficulties in identifying acute illness early (Roland, 2012). An international survey suggests that 80% -90% people in some African countries are not familiar with the term ‘sepsis’, despite the fact that a patient with sepsis is around five times more

likely to die than a patient who has suffered a heart attack or stroke and of those who are, most of them are not aware that sepsis is a leading cause of death (Rubulotta *et al*., 2009). According to Iwashyna *et al*., 2010, too little is known and understood about long-term effects of sepsis, and access to rehabilitation for survivors is poor, despite the evidence that at least one in five survivors suffers long-term physical, cognitive or mental health problem. To address this gap and to decrease the burden of sepsis, in 2013, global sepsis alliance (GSA), and its funding members during the world sepsis declaration day decided to create awareness of sepsis among all stakeholders including members of the public and policy makers and encourage quality improvement initiatives for sepsis recognition and management by hospitals and health care providers. This was said to help in:

1. Reducing sepsis incidence through prevention by at least 20 percent.
2. Improving survival for children and adults.
3. Raising public and professional awareness and understanding of sepsis.
4. Ensuring improved access to adequate rehabilitation services.
5. Creating and maintaining sepsis incidence and outcomes database (Reinhart *et al*., 2013).

Levine *et al*., (2002), highlighted the principal method of primary prevention of sepsis: immunization; as it has been highly successful and cost effective. It is meant to understand that immunization has resulted in the global eradication of small pox and a significant reduction in the prevalence of many infectious diseases (such as poliomyelitis, rubella, tetanus, diphtheria, and measles). In other words, advances in biotechnology have contributes immensely in the improvement of vaccines, including vaccines for *Haemophilus influenzae type b*, *Neisseria meningitides (type c)* and *Streptococcus pneumoniae*. Secondary prevention involves long term antimicrobial prophylaxis with antibiotics, antivirals or antifungal (Van de Watering *et al*., 2013). In order to control sepsis in children, a timely recognition is required first. Quick diagnose and appropriate treatment could determine the patient's outcome (Plunkett and Tong, 2015). This factor must be carried out before a definitive etiological diagnosis is available (Kissoon and Carapetis, 2019). Antibiotic therapy for suspected sepsis should be initiated with broad spectrum antibiotic according to age, group and local epidemiology and administered in doses will help to achieve a bactericidal concentration in the blood. Once a pathogen is identified, the antibiotic regimen should be narrowed and targeted to the isolated bacteria (Folgori and Bielicki, 2019). According to Isa *et al*., (2013), the suspected patient with sepsis should commence the antibiotic therapy within six hours of sepsis diagnosis and within one hour of severe sepsis diagnosis. Souza *et al*., (2017), in their review on epidemiology of sepsis in childhood suggested that, educational efforts aiming to increase the awareness on sepsis by the general public and adhering to the treatment guidelines by health care providers may result in significant improvements in sepsis survival.

**Treatment of Sepsis**

The consistent improvements in survival after sepsis is as a result of effective treatment, though there are still no approved specific molecular therapies for it. Attempts to regularize or boost many aspects of the physiology of patients with sepsis (gas exchange, glucose control, oxygen delivery) have been either ineffective or harmful (Gotts and Matthay, 2016). According to Kelvin, (2023), sepsis can quickly progress to septic shock and death if it's left untreated. However, there are numbers of medication to treat sepsis, including: intravenous (IV) antibiotics to fight the infection, medications to increase blood pressure, insulin to stabilize blood sugar, corticosteroids to reduce inflammation, pain relievers to help with discomfort. Severe sepsis may also require large amounts of IV fluids and a respirator for breathing. Dialysis might be necessary if the kidneys are affected, since kidneys help filter harmful wastes, salt and excess water from your blood. In some cases, surgery may be needed to remove the source of an infection. This may include draining a pus-filled abscess or removing infected tissue. In addition, studies have shown some treatment of sepsis with numerous antibiotics.

Treatment of new born with sepsis has been reported by (Solomon *et al*., 2021). The study showed that among the 119 new born with blood culture confirmed sepsis, 100 (84%) received antibiotics. The remaining percentage was as a result of death among new born occurring shortly after admission parental refusal of antibiotics and discharge from hospital against medical advice. Ampicillin was administered to 95 out of 100 new born. However, among the 83 new born who were administered ampicillin and gentamicin, 72 (87%) had Amp Gen-resistant infections. Eight out of 11 new born treated with ampicillin and cefotaxime had Gram negative bacteria phenotypes resistant to the antibiotic combination. Among the 119 new born with Gram negative sepsis, 30 (25%) died by their 28 days of life. At day 60, 72 (61%) were alive, 43 (36%) dead and 4 (3%) were lost to follow-up and was

compared to Amp Gen-susceptible infections. Amp Gen-resistant infections were associated with higher 28-days (n=2/18, 11%; versus n=28/97, 29%; P= 0.058) and 60-days (n=4/18, 22%; versus n=39/97, 40%; P= 0.074). Though the differences observed were not statistically significant, all caused mortality. In addition, the prevalence of 28-days and 60-days all-cause mortality was significantly higher among new born who had received antibiotics to which their Gram negative bacterial infections were resistant (29% and 41% respectively) compared to those whose treatment corresponded to their infections (0% and 14%, respectively) (P= 0.010, P= 0.028). Their findings were consistent among preterm and term new born, inborn and out born, new born with EOS with LOS, regardless of antibiotic combinations used. A retrospective review of 2700 Canadian patients with septic shock between 1989 and 2004 found that only 50% received effective antibiotics within six hours of the onset of hypotension (Kumar *et al*., 2006). Each hour of delay in antibiotic administration after the onset of shock was connected with a nearly 12% decrease in survival (odds ratio 1.12 per hour delay, 1.103 to 1.136). A more recent retrospective analysis in 2014 of 18 000 patients admitted to 165 ICUs with septic shock or severe sepsis also found that adjusted hospital mortality steadily increased as the delay in antibiotic administration increased (one hour: 25.9%, 24.5% to 27.2%; >6 hours: 33.1%, 30.9% to 35.3%) (Ferrer *et al*., 2014).

The most recent guidelines from the surviving sepsis campaign (SSC) recommend administration of effective intravenous antibiotics within an hour of recognizing severe sepsis or septic shock (Although the exact temporal benefits of antibiotics may be controversial (and unknowable given that a randomized trial would be unethical), there is consensus that effective antibiotics should be given as soon as possible. To meet this goal, hospitals have implemented a variety of screening procedures and protocols to help identify patients with severe sepsis early, rapidly obtain microbiologic samples and administer broad spectrum antibiotics (Dellinger *et al*., 2013).

**Resuscitation:**

Though boosting oxygen delivery improves outcome of patients with sepsis, some methodological issues are also observed (Ronco *et al*., 1993). A study of nine patients with sepsis and nine without in whom care was withdrawn showed that, oxygen delivery threshold for anaerobic metabolism was similar in patients with and without sepsis 3.8 (standard deviation 1.5) Vs 4.5 (1.3) mL/min/Kg; P= 0.28. It was seen to be much lower than expected (Ronco *et al*., 1993). In 2001, Rivers *et al*., published an eagerness waned for increasing oxygen delivery to patients with sepsis. Standard therapy targeted central venous pressure of 8-12 mm Hg, mean arterial pressure of 65-90 mmHg and urine output of 0.5 mL/Kg/h using crystalloid or colloid infusions and vasopressors. 'Early goal directed therapy' (EGDT) targeted the same three parameters as well as central venous oxygen saturation of 70% using red blood cell transfusions and inotropes as required. The EGDT group had a 16% absolute improvement in in-hospital mortality (47% V 31%; relative risk, 0.58, 0.38 to 0.87), thus; was adopted as many centers began using specialized catheters to monitor central venous oxygen saturation continuously.

**Corticosteroid Therapy:**

The use of corticosteroids in the treatment of septic patients has verified to be quite debatable. The presence of glucocorticoids whether endogenous or exogenous is essential for control of the host inflammatory response. Universally, studies have shown high dose steroid regimen increases morbidity and mortality in patients with severe sepsis and in septic shock (Patel and Balk, 2012). Mortality rate has been shown to improve with the use of low dose corticosteroid therapy Annane *et al*., (2002), and is generally considered to be below 300 mg/day (Patel and Balk, 2012). A number of studies showed 28-day mortality rates ranging from 10% to 30% below those of control groups (Patel and Balk, 2012). However, Patel and Balk, (2012); Michard *et al*., (2000), found that low dose corticosteroid treatment of septic patients meaningly enhanced hemodynamic status through an increase in blood pressure and decreased duration of pressure usage. Other studies have found no efficacy toward corticosteroid administration or found increased mortality (Sprung *et al*., 2008; Miller *et al*., 2013). Those observed to have the most benefit from therapy also were found to have adrenal insufficiency. According to Dellinger *et al*., (2013), the Surviving Sepsis campaign has recommended the use of corticosteroid therapy only in the presence of septic shock and only following a failure of blood pressure response to pressure and fluid therapies. The surviving sepsis campaign also recommends hydrocortisone administration at 200 mg/day in these patients and steadily tapering off once pressure therapy is no longer needed to maintain adequate blood pressure. Highly effective antibiotic therapy must be used for children and delays in the provision of care must be minimized. Treatment must be active against the

causative pathogen, safe for the newborn and feasible to deliver reliably in the hospital or community setting (Edmond and Zaidi, 2010). National pediatric associations currently recommend parenteral (intravenous or intramuscular) regimens for new born which are combinations of penicillin/ampicillin and gentamicin or third-generation cephalosporins (e.g., ceftriaxone or cefotaxime) for 10–14 days. These antibiotics are said to be safe and retain effectiveness when given at extended intervals (e.g., twice daily or daily dosing) (Darmstadt *et al*., 2009). These procedures are very active against *Streptococcus spp*., but *Staphylococcus spp*. can be highly resistant (Thaver *et al*., 2009). Gram negative antimicrobial susceptibility to ampicillin and gentamicin can also be poor, especially for *Klebsiella spp*. Emerging *E. coli* resistance to ampicillin, gentamicin and third-generation cephalosporin in intensive care unit in both developed and developing countries is also causing increasing concern (Zaidi *et al*., 2005). According to Darmstadt *et al*., (2009), the potential for important life-threatening toxicity among new born associated with chloramphenicol makes it the least preferred empiric parenteral therapy. Oral antibiotic therapy should be considered in a situation where referral is not possible and there are no health care providers trained to give parenteral antibiotics (Darmstadt *et al*., 2009). It is said to be better than no antibiotics at all. The new second-generation cephalosporins (e.g., cefadroxil and cefuroxime) which are better-absorbed oral antibiotics have an excellent safety profile, a spectrum of activity similar to cotrimoxazole, and may be more effective given the high resistance of newborn pathogens to cotrimoxazole. Ciprofloxacin also is increasingly accepted as safe in new born and permits further investigation for treatment of infections in newborns (Darmstadt *et al*., 2009).

**Conclusion**

According to NICE, (2016), clinicians should take a detailed history to ascertain whether the patient has increased risk factors for sepsis, followed by a thorough physical examination. All emergency departments should have a screening tool and sepsis bundle to aid early identification of the septic child with timely management and appropriate escalation. However, multiple quality improvement projects have demonstrated that the activation of a sepsis bundle is associated with improved outcome in patients with sepsis (Weiss *et al*., 2020; Evans *et al*., 2018).

**REFERENCES**

Adatara, P., Afaya, A., Salia, S. M., Afaya, R. A., Konlan, K. D., Agyabeng-Fandoh, E., Agbinku, E., Ayandayo, E. A., Boahene, I. G. (2019). Risk Factors Associated with Neonatal Sepsis: A Case Study at a Specialist Hospital in Ghana. *The Scientific World Journal*; 9369051.

Adedokun, A. A., Onosakponome, E. O., Nyenke, C. U. (2020). Early Onset and Late Onset of Neonatal Sepsis in a Tertiary Hospital, South-South, Nigeria. *Journal of Advances in Microbiology*; **20**: 19-29.

Agege, E. A., Nwose, E. U., Nwajei, S. D. (2020). Epidemiology and Health Consequences of Early Marriage: Focus on Delta State Nigeria. *International Journal of Community Medicine Public Health*; **7**: 3705-3710.

Agnche, Z., Yenus, Y.H., Abdela, G., K. (2020). Neonatal Sepsis and its Associated Factors among Neonates Admitted to Neonatal Intensive Care Units in Primary Hospitals in Central Gondar Zone, North West Ethiopia, 2019. *Infectious Drug Resistance*; **13**: 3957-3967.

Ahmed, A. S., Chowdhury, M. A., Hoque, M., Darmstadt, G. L. (2002). Clinical and Bacteriological Profile of Neonatal Septicemia in Tertiary Level Pediatric Hospital in Bangladesh. *Indian pediatrics*; **39**(11): 1034-1039.

Akindolire, A. E., Tongo, O., Dada-Adegbola, H., Akinyinka, O. (2016). Etiology of Early Onset Septicemia among Neonates at the University College Hospital, Ibadan, Nigeria. *Journal of Infection in Development Countries*; **10**:1338-1344.

Ako-Nai, A. K., Adejuyigbe, E. A., Ajayi, F. M., Onipede, A. O. (1999). The Bacteriology of Neonatal Septicemia in Ille-Ife, Nigeria. *Journal of tropical Pediatric*; **45** (3): 146 - 15.

Akuirene, O. A., Nwajei, S. D., Adjene, J. O., Ezekiel, U. N. (2020). Epidemiology of Respiratory Distress in Pregnancy and the Newborn in Delta State, Nigeria. *International Journal of Community Medicine and Public Health*; **7**: 3705-3710.

Alvarez-Marin, R., Lepe, J. A., Gasch-Blasi, O., Rodriguez- Martinez, J. M., Calvo-Montes, J., Lara-contreras, R., Martin-Gandul, C., Tubau-Quintano, F., Cano-Garcia, M. E., Rodriguez-Lopez, F., Rodriguez Bano, J., Pujol-Rojo, M., Torre-Cisneros, J., Martinez-Martinez, L., Pascual-Hernandez, A., Jimenez-Mejias M.E. (2021). Clinical Characteristics and Outcome of Bacteraemia caused by *Enterobacter cloacae* and *Klebsiella aerugenes*: More Similarities than Differences. *Journal of Global Antitmicrobial Resistant*; **25**: 351- 358.

American Thoracic Society; Infectious Diseases Society of America. (2005). Guidelines for the Management of Adults with Hospital-Acquired, Ventilator-Associated, and Healthcare-Associated *pneumonia*. *American Journal of Respiratory and Critical Care Medicine*; **171**(4): 388-416.

Andreola B, Bressan S, Callegaro S, Liverani A, Plebani M, Da Dalt L. ( 2007). Procalcitonin and C-Reactive Protein as Diagnostic Markers of Severe Bacterial Infections in Febrile Infants and Children in the Emergency Department. *Pediatric Infectious Disease Journal*; **26**(8):672-677.

Annane, D., Sébille, V., Charpentier, C., Bollaert, P. E., François, B., Korach, J. M., Capellier, G., Cohen, Y., Azoulay, E., Troché, G., Chaumet-Riffaud, P., Bellissant, E. (2002). Effect of Treatment with low doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock. *Journal of the American Medical Association*; **288**(7):862-71. doi: 10.1001/jama.288.7.862.

Ayukekbong, J. A., Ntemgwa, M., Atabe, A. N. (2017). The Threat of antimicrobial resistance in developing countries: Causes and control strategic. Antimicrobial Resistant infection and control **6**:47.

Baharoon, S., Telmesani, A., Tamim,H., Alsafi, E., Aljohani, S., Mahmoud, E., Aj-Jahdali, H. (2015). Community- Versus Nosocomial-Acquired Severe Sepsis and Septic Shock in Patients Admitted to a Tertiary Intensive Care in Saudi Arabia, Etiology and Outcome. Journal of Infection and Public Health; **8**(5): 418-424.

Baraff, L. J., Bass, J. W., Fleisher, G. R., Klein, J. O., McCracken, G. H. Jr., Powell, K. R., Schriger, D. L. (1993). Practice Guideline for the Management of Infants and Children 0 to 36 Months of Age with Fever without Source. Agency for Health Care Policy and Research. *Annals of Emergency Medicine*; **22**(7): 1198-1210.

Barochia, A. V., Cui, X., Vitberg, D., Suffredini, A. F., o'Grady, N. P., Banks, S. M., Minneci, P., Kern, S. J., Danner, R. L., Natanson, C., Eichacker, P. Q. (2010). Bundled Care for Septic Shock: An Analysis of Clinical Trials. *Critical Care Medicine*; **38**(2): 668-678.

Bauer, M., Gerlach, H., Vogelmann, T., Preissing, F., Stiefel, J., Adam, D. (2020). Mortality in Sepsis and Septic Shock in Europe, North America and Australia between 2009 and 2019 Results from a Systematic Review and Meta-Analysis. *Critical Care*; **24**(1): 239

Bayana, E., Endale, K., Akuma, A., Terfa, Y., Tegenu, K. (2020). Neonatal Sepsis among Neonates at Public Hospitals in Jimma, Ethiopia. *International Journal of Pediatric*; **8**: 12011-12021.

Bech, C.M., Stensgaard, C.N., Lund, S., Holm-Hansen, C., Brok, J.S., Nygaard, U., Poulsen, A. (2022). Risk Factors for Neonatal Sepsis in Sub-Saharan Africa: A Systematic Review with Meta-Analysis. *British Medical Journal*; e054491.

Bergsten, G., Samuels-Son, M., Wult, B., Leijonhufvud, I., Fischer, H., Svanborg, C. (2004). PapG-Dependent Adherence Breaks Mucosal Inertia and Triggers the Innate Host Response. *Journal of Infectious Disease*; **189**: 1734-1742.

Beshah D. Desta A. Belay G. Abede T. Gebreselasie, S., Tessema, T. S. (2022). Antimicrobial Resistance and Associated Risk Factors of Gram Negative Bacterial Blood Stream Infections in Tikur Anbessa Specialized Hospital, Addis Ababa. *Infection and Drug Resistance*; **15**: 5043-5059.

Birrie, E., Sisay, E., Tibebu, N.S., Tefera, B. D., Zeleke, M., Tefera, Z. (2022). Neonatal Sepsis and Associated Factors among Newborns in Woldia and Dessie Comprehensive Specialized Hospitals, North-East Ethiopia, 2021. *Infection and Drug Resistance*; **15**: 4169-4179.

Breijyeh, Z., Jubeh, B., Karaman, R. (2020). Resistance of Gram-Negative Bacteria to Current Antibacterial Agents and Approaches to Resolve it. *Molecules*; **25** (1340): 1-23.

Canzoneri, C. N., Akhavan, B. J., Tosur, Z. Andrade, P. E. A., Aisenberg G. M. (2017). Follow-up Blood Cultures in Gram-Negative Bacteria: are they needed? *Clinical Infectious Disease;* **65**: 1776-1779.

Cardoso, T., Almeida, M., Friedman, N. D., Aragao, I., Costa-Pereira, A., Sarmento, A.E., Azevedo, L. (2014). Classification of Healthcare-Associated Infection: A Systematic Review 10 Years after the first Proposal. *Bio-Medical Central Medicine*; 12:40.

Carroll, M., Rangaihagari, A., Musabeyezu, E., Singer, D., Ogbuagu, D. (2016). Five Year Antimicrobial Susceptibility Trends among Bacterial Isolates from a Tertiary Health-Care Facility in Kigali, Rwanda. *American Journal of Tropical medicine Hygiene*; **95** (6): 1277-1283.

Centre for Disease Control and Prevention (CDC). (2019. Antibiotics Resistance Threats in the United States, Atlanta GA: United States Department of Health and Human Services. Accessed: 31st October 2022. www.cdc.gov/DrugdResistance /Biggestthreats.html

Chukwumeze, F., Lenglet, A., Olubiyo, R., Lawal, A.M., Oluyide, B., Oloruntuyi, G., Ariti, C., Gomez, D., Roggeveen, H., Nwankwo, C., Augustine, N.A., Egwuenu, A., Maloba, G., Sherlock, M., Muhammad, S., Wertheim, H., Hopman, J., Clezy, K. (2021).

Clyne, B., Olshaker, J. S. (1999). The C-Reactive Protein1. *Journal of Emergency Medicine*; **17**(6): 1019- 1025.

Cruz, A. T., Mahajan, P., Bonsu, B. K., Bennett, J. E., Levine, D. A., Alpern, E. R., Nigrovic, L. E., Atabaki, S. M., Cohen, D. M., VanBuren, J. M., Ramilo, O., Kuppermann, N., Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network. (2017). Accuracy of Complete Blood Cell Counts To Identify Febrile Infants 60 Days Or Younger With Invasive Bacterial Infections. *Journal of the American Medical Association Pediatric*; **171**(11): e172927.

Cruz, A. T., Lane, R. D., Balamuth, F., Aronson, P. L., Ashby, D. W., Neuman, M. I., Souganidis, E. S., Alpern, E. R., Schlapbach, L. J. (2020). Update on Pediatric Sepsis. Infectious Disease. Review Article; *Wiley*, *Journal Of American College Of Emergency Physicians Open;* **1**(5):981-993.

Darmstadt, G. L., Batra, M., Zaidi, A. K. (2009). Oral Antibiotics in the Management of Serious Neonatal Bacterial Infections in Developing Country Communities. *Pediatric Infectious Disease Journal*; **28**(1): S31-6.

Davin-Regli, A. (2015). *Enterobacter aerogenes* and *Enterobacter cloacae*; Versatile Bacterial Pathogens Confronting Antibiotic Treatment. *Frontier Microbiology*; 6, 392.

Deep, A., Duncan, C. (2023). Sepsis in Children. *Epocrates.* Accessed 21st March, 2023. https://Online.Epocrates.Com>Diseases>Guidelines

De S,Williams, G. J., Hayen, A., Macaskill, P., McCaskill, M., Isaacs, D., Craig, J. C. (2014). Value of White Cell Count in Predicting Serious Bacterial Infection in Febrile Children Under 5 Years of Age. *Archives of Disease in Childhood*; **99**(6):493-499.

De Souza, D., Machado, F. (2019). Epidemiology of Pediatric Septic Shock. *Journal of*

*Pediatric Intensive Care*. **8**(1): 3-10.

Dhir, S. K., Sundaram, V., Gautam, V., Munda, V. S., Tiewsoh, J. B. A., Angurana, S. K., Kumar, Saini, S., Dutta, S., Kumar, P. (2021). Microorganisms Profile and Antimicrobial Resistance Pattern in out born Neonates in Northern India: A Hospital Based Observation Study. *Journal of Tropical Pediatrics*; **67**(3), 1-9.

Diekema, D. J., Beekmann, S. E., Chapin, K. C., Morel, K. A., Munson, E., Doern, G. V. (2003) Epidemiology and Outcome of Nosocomial and Community-Onset Blood Stream Infection. *Journal of Clinical Microbiology* ; **41**(8): 3655-3660.

Digiacinto, J., Johnson, S. (2021) Septic Shock. Headline. Accessed: 10th march, 2023. https://www.healthline.com/health/septic-shock.

Downes, K. J., Fitzgerald, J. C., Weiss, S. L. (2020). Utility of Procalcitonin as a Biomarker for Sepsis in Children. *Journal of Clinical Microbiology*; **58**(7): e01851-19.

Dugani, S., Kisson, N. (2017). Global Advocacy Needed for Sepsis in Children. *Journal of Infection;* **74**: S6, 1-5.

Edmond, K., Zaidi, A. (2010). New Approaches to Preventing, Diagnosing, and Treating Neonatal Sepsis. *PLOS Medicine*; **7**(3):e1000213.

Endale, T., Fentahun, N., Gemada, D., Hussen, M.A. (2016). Maternal and Fetal Outcomes In Term Premature Rupture of Membrane. *World Journal of Emergency Medicine*; **7**:147-152.

Ershad, M., Mostafa, A., Dela Cruz, M. (20190 Neonatal Sepsis. *Current Emergency and Hospital Medicine Reports*. **7** (3):83-90.

Evans, I. V. R., Phillips, G. S., Alpern, E. R., Angus, D. C., Friedrich, M. E., Kissoon, N., Lemeshow, S., Levy, M. M., Parker, M. M., Terry, K. M., Watson, R. S., Weiss, S. L., Zimmerman, J., Seymour, C.W. (2018). Association between the New York Sepsis Care Mandate and In-Hospital Mortality for Pediatric Sepsis. *Journal of the American Medical Association*; **320**(4):358-367.

Ferrer, R., Artigas, A., Levy, M. M., Blanco, J., Gonzalez-Diaz, G., Garnacho-Montero, J., Ibanez, J., Palencia, E., Quintana, M., Delatorre-Prados, M.V. (2008). Educational Sepsis Study Group. Improvement in Process of Care and Outcome after a Multicenter Severe Sepsis Educational Program in Spain. *Journal of American Medical Association*; **299**(19): 2294-2303.

Ferrer, R., Martin-Loeches, I., Phillips, G., Osborn, T. M., Townsend, S., Dellinger, R. P., Artigas, A., Schorr, C., Levy, M. M. (2014). Empiric Antibiotic Treatment Reduces Mortality in Severe Sepsis and Septic Shock from the First Hour: Results from a Guideline-Based Performance Improvement Program. *Critical Care Medicine*; **42**(8):1749-55.

Fleischmann, C., Reinhart, F., Cassini, A., Horner, R., Harder, T., Markwart, R., Trondle, M., Savova, Y., Kissoon, N., Schlattmann, P., Reinhart, K., Allergranzi, 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.

Folgori, L., Bielicki, J. (2019). Future Challenges in Pediatric and Neonatal Sepsis: Emerging Pathogens and Antimicrobial Resistance. *Journal of Pediatric Intensive Care*; *Review Article* **17**(8): 17-24.

Friedman, N. D., Kaye, K. S., Stout, J. E., Mcgarry, S. A., Trivette, S. L., Briggs, J. P., Lamm, W., Clark, C., MacFarquhar, J., Walton, A. L., Reller, L. B., Sexton, D. J. (2002). Health Care-Associated Bloodstream Infections in Adults: A Reason to Change the Accepted Definition of Community-Acquired Infections. *Annals of Internal Medicine*; **137**(10): 791-797.

Gao, J. F., Guan, X., Zhu, L., Zang, L., Xu, X., Chang, C. Y., Liu, H. (2019). Incidence, Bacterial Profiles, and Antimicrobial Resistance of Culture-proven Neonatal Sepsis in South China. *Infection and Drug Resistance*. 12, 3797 – 3805.

Garcia-Alvarez, M., Marik, P., Bellomo, R. (2014). Sepsis-Associated Hyperlactatemia. *Critical Care*; **18**(5): 503.

Garcia-Prats, J. A., Cooper, T. R., Schneider, V. F., Stager, C. E., Hansen, T. N. (2000). Rapid Detection of Microorganisms in Blood Cultures of Newborn Infants Utilizing an Automated Blood Culture System. *Pediatrics*; **105**(3 Pt 1): 523-7.

Garrod, D., Beale, V., Rogers, J., Miller, A. (2011). Midwifere. *International Journal of Obstetrics and Gynaecology*. *Supplement Journal*; **118**(1): 149-157.

Gauer, R. L. (2013). Early Recognition and Management of Sepsis in Adults: The First Six Hours *American Family Physician*; **88**(1): 44-53.

Gebremedhin, D., Berhe, H., Gebrekirstors, K., Warbuton, D. (2016). Risk Factors for Neonatal Sepsis in Public Hospitals of Mekelle City, North Ethiopia, 2015. Unmatched Case Control Study. *PLOS ONE*; **11**(6): e0154798.

Georgios, F., Evangelos, L., Aikaterini, S., Nikoletta, S., Sophia, M., Aikaterini, V., Maria, M., konstantinos, V., Stavroula, P., Emmanouil, K. (2019). A 2-Year Single-Centre Audit on Antibiotics Resistance of *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *klebsiella pneumonial* Strains from an Intensive Care Unit and other wards in a General Public Hospitals in Greece. *Multi-disciplinary Digital Publishing Institute*. **8**(62): 1-2.

Godfrey, E., Majaliwa, E., Assenga, E.N. (2022). Aetiology, Antimicrobial Susceptibility and Outcome of Children with Sepsis Admitted at Muhimbili National Hospital, Dar es Salaam. *Pan African Medical Journal*; **42**(167).

Goldstein, B., Giroir, B., Randolph, A. (2005). International Consensus Conference On Pediatric Sepsis. International Pediatric Sepsis Consensus Conference: Definitions for Sepsis and Organ Dysfunction in Pediatrics. *Pediatric Critical Care Medicine*; **6**(1):2-8

Guo-Yun, S., Chao-Nan, F., Bo-Liang, F., Zheng-De, X., Su-Yun, Q. (2022). Comparison of Hospital- and Community-Acquired Septic Shock in Children: A Single-Center, Cohort, Retrospective Study. *World Journal of Pediatrics*; 18(11): 734-745.

Gomez, B., Mintegi, S., Bressan, S., Da Dalt, L., Gervaix, A., Lacroix, L., European Group for Validation of the Step-by-Step Approach. (2016). Validation of the "Step-Bystep" Approach in the Management of Young Febrile Infants. *Pediatrics*; **138**(2): Pii:e20154381.

Gotts, J. E., Matthay, M. A. (2016). Sepsis: Pathophysiology and Clinical Management. *British Medical Journal*; **353**:i1585.

Gupta, S., kashyap, B. (2016). Bacteriological Profile and Antibiogram of Blood Culture Isolates from a Tertiary Care Hospital of North India. *Tropical Journal of Medical Research*; **19**(2): 94-99.

Hall, M. J., Williams, S.N., De-Frances, C. J., Golosinskly, A. (2011). Impatient Care for Septicemia or Sepsis: A Challenge for Patients and Hospitals. National Center for Health Statistics (NCHs). Hispanic Community Health Study. *Data Brief*; (62): 1-8.

Hassan-Hanga, F., Ibrahim, B. S., Kabir, H., Ibrahim, U. H., Abdulsalam, K., Ahmed, Z. D., Kabara, H. S., Gaya, S. A., Haliru, D.G., Sadiq, N.M., Inuwa, S., Mohammad, M.A. (2022). Assessing Predictors of Mortality Among Children Admitted with Sepsis at a Referral Tertiary Health Center, Northwestern Nigeria. 1-24.

Hartman, M. E., Linde-Zwirble, W. T., Angus, D. C., Watson, R. S. (2013). Trends in the Epidemiology of Pediatric Severe Sepsis. *Pediatric Critical Care Medicine* ; **14**(7): 686-693.

Ho, J., Tambyah, P. A., Paterson, D. L. (2010). Multi Resistance Gram-negative Infections: A

Global Perspective. Current Opinion on Infectious Disease; **23**(6): 546-553.

Hoenigl, M., Wagner, J., Raggam, R.B., Prueller, F., Prattes, J., Eigl, S., Leitner, E., Hönigl, K., Valentin, T., Zollner-Schwetz, I., Grisold, A.J., Krause, R. (2014). Characteristics of Hospital-Acquired and Community-Onset Blood Stream Infections, South-East Austria. *PLOS ONE*; **9**(8): e104702.

Holmes, C. L., Anderson, M. T., Mobley, H. L. T., Bachman, M. A. (2021). Pathogenesis of Gram-Negative Bacteraemia. *Clinical Microbiology Reviews*; **34**(2): e00234-20.

Holt, K. E., Baker, S., Dongol, S., Basnyat, B., Adhikan, N., Thorson, S., Pulickal, A. S., Song, Y., Parkhill, J., Farrar, J.J., Murdoch, D.R., Kelly, D.F., Pollard, A.J., Dougan, G. (2010). *Biomedicine Central Infectious Diseases;* **10**:144.

Humoodi, M. O., Aldabbagh, M. A., Salem, M. M., Al Talhi, Y. M., Osman, S. M., Bakhsh, M., Alzahrani, A. M., Azzam, M. (2021). Epidemiology of Pediatric Sepsis in the Pediatric Intensive Care Unit of King Abdulazic. Medical City, Jeddah, Saudi Arabia. *Biomedical Center of Pediatrics*; **21**: 222.

Isa, S. E, Onyedibe, K., Iroezindu, M. O., Egah, D. Z. (2013). An Audit of Diagnosis and Treatment of Sepsis in North-Central Nigeria. *Nigeria Journal of Medicine*; **229**(4): 1115-2613.

Isa, S. E., Iroezindu, M. O., Awang, S. K., Simji, G. S., Onyedibe, K. I., Mafuka, Egah, D. Z., Crook, D. (2013). An Audit of Diagnosis and Treatment of Sepsis in North-Central, Nigeria. *Nigerian Journal of Medicine*; **22**(4): 319-25.

Iwashyna, T. J., Ely, E. W., Smith, D. M., Langa, K. M. (2010). Long-Term Cognitive Impairment and Functional Disability among Survivors of Severe Sepsis. *Journal of American Medical Association*; **304**(16): 1787-1794.

Jaramillo-Bustamante, J. C., Marin-Agudelo, A., Fernandez-Laverde, M., Bareno-Silva, J. (2012). Epidemiology of Pediatric Intensive Care Units: First Colombian Multi-Center Study. *Pediatric Critical Care Medicine*; **13**(5): 501-508.

Jean, C., Vincent, J., Stephen, H., Andreas, V., Herman, G., Pittet, D. (2012). Ready for a world without Antibiotics?. The Pensieres Antibiotic Resistance Call to Action. *American Infection Control*; **1**(11): 1-13.

John, B., David, M., Mathias, L., Elizabeth, N. (2015). Risk Factors and Practices Contributing to Newborn Sepsis in a Rural District of Eastern Uganda, August 2013: A Cross Sectional Study. *Bio Medical Central Research Notes*; **8**: 339.

Joshi, S. J., Ghole, V. S., Niphadkar, K. B. (2000). Neonatal Gram Negative Bacteriema. *India Journal of Pediatric*. **67** (1): 27 – 32.

Kabwe, N., Tembo, J., Chilukulu, L., Chilufya, M., Ngulube, F., Lukwesa, C., Kapasa, M., Enne, V., Wexner, H., Nwananyanda, L., Hamer, D.H., Sinyangwe, S., Ahmed, Y., Klein, N., Maeurer, M., Alimuddin, Z., Bates, M. (2016). Etiology, Antibiotic Resistance and Risk Factors for Neonatal Sepsis in a Large Referral Center in Zambia. *The Pediatric Infectious Disease Journal*; **35**: e191-e198.

Khan, M. R., Maheshwari, P. K., Masood, K., Qamar, F. N., Haque, A. U. (2012). Epidemiology and Outcome of Sepsis in a Tertiary Care Pediatric Intensive Care Unit of Pakistan. *Indian Journal of Pediatric*; **79**(11): 1454-1458.

Keeley, A. J., Nsutebu, E. (2021). Improving Sepsis Care in Africa: An Opportunity for Change?. *Pan African Medical Journal*: **40**(204).

Kelvin, M. (2023). Sepsis Symptoms, Causes and Recovery. Sepsis: Symptoms, Causes, Treatment, Risk, and More (Healthline.Com). Accessed: 12/03/2023. https://www.Healthline.Com/Health/Sepsis

Kenneth, I. O., Thomas, F. B., Nwadike, V., Afolaranmi, T., Okolo, M. O., Uket, O., Diala, U. M., Da'am, C. K., Egah, D. Z., Banwat, E. B. (2015). High Rate of Bacteria Isolates of Neonatal Sepsis with Multidrug Resistance Patterns in Jos Nigeria. Annals

of Pediatrics and child Health. **3**(2): 1052. https://www.academia.edu/es/70598560/High_Rates_of_Bacteria_Isolates_of_Neonatal_Sepsis_with_Multidrug_Resistance_Patterns_in_Jos_Nigeria.

Kim, F., Polin, R. A., Hooven, T. A. (2020). Neonatal Sepsis. *British Medical Journal*; **371**: m3672.

Kissoon, N., Carcillo, J. A., Espinosa, V., Argent, A., Devictor, D., Madden, M., Singhi, S., Van Der Vort, E., Latour, J. (2011). Global Sepsis Initiative Vanguard Center Contributors. Sepsis Initiative. *Pediatric Critical Care Medicine*; **12**(5): 494-503.

Kissoon, N., Carapetis J. (2019). Pediatric Sepsis in the Developing world. *Journal of Infection;* **7**(1): S21-S26.

Kumar, A., Roberts, D., Wood, K.E., Light, B., Parrillo, J.E., Sharma, S., Suppes, R., Feinstein, D., Zanotti, S., Taiberg, L., Gurka, D., Kumar, A., Cheang, M. (2006). Duration of Hypotension before Initiation of Effective Antimicrobial Therapy is the Critical Determinant of Survival in Human Septic Shock. *Critical Care Medicine*; **34**(6):1589-96.

Kuppermann, N., Dayan, P.S., Levine, D.A., Vitale, M., Tzimenatos, L., Tunik, M.G., Saunders, M., Ruddy, R. M., Roosevelt, G., Rogers, A. J., Powell, E. C., Nigrovic, L. E., Muenzer, J., Linakis, J. G., Grisanti, K., Jaffe, D.M., Hoyle, J.D. Jr., Greenberg, R., Gattu, R., Cruz, A. T., Crain, E. F., Cohen, D. M., Brayer, A., Borgialli, D., Bonsu, B., Browne, L., Blumberg, S., Bennett, J.E., Atabaki, S. M., Anders, J., Alpern, E. R., Miller, B., Casper, T.C., Dean, J.M., Ramilo, O., Mahajan, P., Febrile Infant Working Group of the Pediatric Emergency Care Applied Research Network (PECARN). (2019). A Clinical Prediction Rule to Identify Febrile Infants 60 Days and Younger at Low Risk for Serious Bacterial Infections. *Journal of the American Medical Association Pediatric*; **173**(4): 342-351.

Lambert, V., Matthews, A., Macdonell, R., Fitzsimons, J. (2017). Paediatric Early Warning Systems for Detecting and Responding to Clinical Deterioration in Children: A Systematic Review. *British Medical Journal Open*; 7(3): E014497.

Lamping, F., Jack, T., Rubsamen, N., Sasse, M., Beerbaum, P., Mikolajczyk, R. T., Boehne, M., Karch, A. (2018). Development and Validation of a Diagnostic Model for Early Differentiation of Sepsis and Non-Infectious SIRS in Critically Ill Children- A Data-Driven Approach using Machine learning Algorithms. Bio-Medical Central Pediatric; **18**(1): 112.

Lanziotti, V. S., Póvoa, P., Soares, M., Silva, J. R., Barbosa, A. P., Salluh, J. I. (2016). Use of Biomarkers in Pediatric Sepsis: Literature Review. *Revista Brasileira de Terapia Intensiva* **28**(4):472-482.

Lee, A; Mirrett, S., Reller, L. B., Weinstein, M. P. (2007) Detection of Bloodstream Infection in Adult; How Many blood Cultures are needed? *Journal of Clinical Microbiology*; **45**(11): 3546-3548.

Le-Doare, K., Bielicki, J., Health, P. T., Sharland, M. (2015). Systemic Review of Antibiotic Resistance Rates among Gram-Negative Bacteria in Children with Sepsis in Resource Limited countries. *Journal of the Pediatric infectious Diseases Society*; **4**(1):11-20.

Lenz, R., Leal, J. R., Church, D. L., Gregson, D. B., Ross, T., Laupland, K. B. (2012). The Distinct Category of Healthcare Associated Bloodstream Infections. *Bio-Medical Central and Infectious Disease*; **12**: 85.

Levi, M., Toh, C. H., Thachil, J., Watson, H. G. (2009). Guidelines for the Diagnosis and Management of Disseminated Intravascular Coagulation. British Committee for Standards in Haematology. *British Journal of Haematology*; **145**(1): 24-33.

Levine, M. M., Campbell, J. D., Kotloff, K. L. (2002). Overview of Vaccines and Immunization. British Medical Bulletin; **62**: 1-13.

Levy, M. M., Dellinger, R. P., Townsend, S. R., Linde-Zwirble, W. T., Marshall, J. C., Bion, J., Schorr, C., Artigas, A., Ransay, G., Beale, R., Parker, M. M., Gerlach, H., Reinhart, K., Silvia, E., Harvey, M., Regan, S., Angus, D.C. (2010). Surviving Sepsis Campaign. The Surviving Sepsis Campaign: Results of an International Guideline-Based Performance Improvement Program Targeting Severe Sepsis. *Critical Care Medicine*; **38**(2): 367-374.

Liu, I., Oza, S., Hogan, D., Perin J., Rudan, I., Lawn, J. E., Cousens, S., Mathers C., Black, R. E. (2o15). Global, Regional and National Causes of Child Mortality in 2000-2013 with Projection to Inform Post-2015 Priorities: An Updated Systematic Analysis. *Lancet*. **385**(9966): 430-440.

Medugu, N., Iregbu, K. C., Iron, T. P. (2018). Aetiology of Neonatal Sepsis in Nigeria and relevance Groups b *Streptococcus* : A Systematic Review. *PLOS ONE;* **13**(7): e0200350.

Macrae, D., Grieve, R., Allen, E., Sadique, Z., Morris, K., Pappachan, J., Parslow, R., Tasker, R. C., Elbourne, D., CHiP Investigators. (2014). A Randomized Trial of Hyperglycemic Control in Pediatric Intensive Care. *New England Journal of Medicine*; **370**(2): 107-18.

Magill, S. S., Edwards, J. R., Bamberg, W., Beldavs, Z. G., Dumyati, G., Kainer, M. A., Lynfield, R., Maloney, M., Mcallister-Hollod, L., Nadle, J., Ray, S. M., Thompson, D. L., Wilson, L. E., Fridkin, S. K. (2014). Emerging Infection Program Healthcare-Associated Infections and Antimicrobial use Prevalence Survey Team. Multistate Point-Prevalence Survey of Health Care-Associated Infections. *The New England Journal of Medicine*; **370**(13): 1198-1208.

Mahajan, P., Grzybowski, M., Chen, X., Kannikeswaran, N., Stanley, R., Singal, B., Hoyle, J. Jr., Borgialli, D., Duffy, E., Kuppermann, N. (2014). Procalcitonin As a Marker of Serious Bacterial Infections in Febrile Children Younger Than 3 Years Old. *Academic Emergency Medicine*; **21**(2): 171-179.

Mahavanakul, W., Nickerson E. K., Srisomang, P., Teparrukku L, P., Lorvinitnun, P., Wongyingsinn, M., Chierakul, W., Hong Suwan, M., West, T.E., Day, N.P., Limmathurotsakul, D., Peacock, S.J. (2012). Feasibility of Modified Surviving Sepsis Campaign Guidelines in a Resource Restricted Setting Based on a Cohort Study of Severe *S. aureus* Sepsis [Corrected]. *PLOS ONE*; **7**(2): e29858.

Manchanda, V., Bhalla, P., Sethi, M., Sharma, V. K. (2006). Treatment of Enteric Fever in Children on the Basis of Current Trends of Antimicrobial Susceptibility of *Salmonella Enterica Seovar typhi* and paratyphi. *American Indian Journal of Medical Microbiology*; **24**: 101-102.

Mangia, C. M., Kissoon, N., Branchini, O. A., Andrade, M. C., Kopelman, B. I., Carcillo, J. (2011). Bacteria Sepsis in Brazilian Children: A Trend Analysis. *PLOS one*; **6**(6): e14817.

Marchetti, O., Calandra, T. (2015). Infection in the Neutropenic Cancer Patient., Bacterial Infectious Disease (*Third Edition* ). *Infectious Disease*; 1, 804-820.

Martin, E., Sanjay, B., Barbel, C., Jurgen, G., Peter, G. B., Phillippe, H., Peter, H., Carola, I., Axel, K., Elaine L., Wolfgang, M. Martin, M., Peter, O., Birgit, R., Manfred, R., Ricardo, M., Schmithausen, H-G., Sonntag, M.T. (2017). Antibiotic Resistance: What is so special about Multi Driug-Resistant Gram-Negative Bacteria. *German Medical Science Hygiene and Infection Control*; **12**: 1-24.

Mayo Clinic (2023). Sepsis-Symptoms and Causes; Complications of Sepsis. https://www.mayochoic.org>sepsis Accessed : 12/03/2023.

Mayr, F. B., Yende, S., Angus, D. C. (2014). Epidemiology of Severe Sepsis. *Virulence;* **5**:4-11.

Meremikwu, M. M., Nwachukwu, C. E., Asuquo, A. E., Okebe, J. U. (2005). Bacterial Isolates from Blood Cultures of Children with Suspected Septicaemia in Calabar, Nigeria. *Bio-Medical Centre of Infectious Disease*; **5**: 110.

Merell, D. S., Falkow, S. (2004). Frontal and Stealth Attack Strategies in Microbial Pathogenesis: *Nature*; **430**: 250-256.

Mia, A. R., Zenn, T. (2020). Antibiogram of Blood Culture lsolates from a Hospital in Dhaka, Bangladesh. *Matrix science medicine*; **4**(1): 1-5.

Michard, F., Boussat, S., Chemla, D., Anguel, N., Mercat, A., Lecarpentier, Y., Richard, C., Pinsky, M. R., Teboul, J. L. (2000). Relation Between Respiratory Changes in Arterial Pulse Pressure and Fluid Responsiveness in Septic Patients with Acute Circulatory Failure. *American Journal of Respiratory Critical Care Medicine*; **162**(1): 134-8.

Miller, R. R. 3rd, Dong, L., Nelson, N. C., Brown, S. M., Kuttler., K. G., Probst, D. R., Allen, T. L., Clemmer, T. P. (2013). Intermountain Healthcare Intensive Medicine Clinical Program. Multicenter Implementation of a Severe Sepsis and Septic Shock Treatment Bundle. *American Journal of Respiratory Critical Care Medicine*; **188**(1): 77-82.

Mut Lu, M., Aslan, Y., Hekimoglu, B., Yilmaz, G. (2011). Neonatal Sepsis Caused by Gram-Negative Bacteria in a Neonatal Intensive Care Unit: A Six Years Analysis. *Hong Kong Journal of Pediatrics*; **16**(4): 253-257.

National Institute for Health and Care Excellence (NICE) (2016). Overview Sepsis: Recognition, Diagnosis and Early Management Guidance Https://Www.Nice.Org.Uk/Guidance/Ng51/Resources/Sepsis-Recognition-Diagnosis-and-Early-Management-1837508256709. Accessed 14 February 2023.

Nwankwor, O. C., McKelvie, B., Frizzola, M., Hunter, K., Kabara, H. S., Oduwole, A., Oguonu, T., Kissoon, N. (2019). A National Survey of Resources to Address Sepsis in Children in Tertiary Care Centers in Nigeria. *Frontiers in pediatrics*; **7**: 234. https://www.frontiersin.org/articles/10.3389/fped.2019.00234/full

Nwadioha, S. I., Kashibu, E., Alao, O. O., Aliyu, I. (2011). Bacterial Isolates in Blood Cultures of Children with Suspected Septicaemia in Kano: A Two Year Study. *Niger Postgard Medicinal Journal*; **18**: 130-133.

Odetola, F., Gebremariam, A., Freed, G. L. (2007). Patient and Hospital Correlate of Clinical Outcomes and Resource Utilization in Severe Paediatric Sepsis. *Paediatrics*; **119**: 487-494.

Ogbara, C. N., Chime, H.E., Nwose, E. U. (2021). Neonatal sepsis in Nigeria 1: Introductory Overview. *Journal of Scientific and Technical Research*; **36**(2): 2574-1241.

Ogbara, C. N., Chime, H. E., Nwose, E. U. (2021). Neonatal Sepsis in Nigeria 2: Narrative Review of Epidemiology and Socioeconomic Factors. *Journal of Scientific and Technical Research*; **36**(2): 2574-1241.

Ogbolu, D. O., Piddock L. J. V., Webber, M. A. (2019). Opening Pandora's Box: High Level Resistance to Antibiotics of Last Resort in Gram-Negative Bacteria from Nigeria. *Journal of Global Antimicrobial Resistance*; **21**(2020): 211-217.

Ogundare, E., Akintayo, A., Aladekomo, T., Adeyemi, L., Ogunlesi, T., Oyelami, O. (2019). Presentation and Outcomes of Early and Late Onset Neonatal Sepsis in a Nigerian Hospital. *African Health Sciences*; **19**(3): 2390-2399.

Ogundare, E.O., Akintayo, A.A., Dedeke, I.O.F., Okeniyi, J.A., Adeyemi, L.A., Ogunlesi, T.A., Oyelame, O.A. (2016). Neonatal Septicaemia in a Rural Nigerian Hospital: Aetiology, Presentation and Antibiotic Sensitivity Pattern. *British Journal of Medicine and Medical Research* **12**(7): 1-91.

Ogunkunle, T. O, Abdulkadir, M. B., Bello, S. O., Raheem, R. A., O'laosebikan, R. (2022). Pediatric Blood Culture Isolates and Antibiotic Sensitivity Pattern in a Nigerian Tertiary Hospital. *Nigerian Journal of Medicine*; **29**(2): 261-264.

Oliphant C. M., Eroschenko, K. (2015). Antibiotic Resistance, Part 2: Gram-Negative Pathogens. *Journal of Nurse Practice*; **11**(1): 79-86.

Oliva, A., Carmon, A., Y., de La C Lopez, E., Alvarez, R., Aung, M. S., Kobayashi, N., Quinones, D. (2021). Characterization of Neonatal Infection by Gram Negative *Bacilli* and Associated Risk Factors, Havana, Cuba. Multidisciplinary Digital Publishing Institute; Infectious Disease Reports; **13**(1): 219-229.

Olorukooba, A. A., Ifusemu, W. R., Ibrahim, M. S., Jibril, M. B., Amadu, L., Lawal, B. B. (2020). Prevalence and Factors Associated with Neonatal Sepsis in a Tertiary Hospital, North West Nigeria. *Nigerian Medical Journal;* **61**(2): 60-66.

Olowo-Okere, A., Ibrahim Y. K. E., Nabti., L. Z., Olayinka, B. O. (2020). High Prevalence of Multi-Drug Resistant Gram-Negative Bacterial Infections in Northwest Nigeria. *Germs*; **10**(4): 310-321.

Onipede, A. O., Onuayade, A. A., Elusiyan, J. B., Obiajunwa, P. O., Ogundare, E. O., Olaniran, O. O., Adeyemi, L. A., Oyelami, O. O. (2009). Invasive Bacteria Isolates from Children with Severe Infections in a Nigerian Hospital. *Journal of Infection in Developing Countries*; **3**(6): 429-436.

Onubogu, U. C., West, B. M. (2022). Pattern and Outcome of Diseases among Children Presenting in the Emergency room of a Tertiary Hospitals in Port Harcourt, Nigeria. *Open Journal of Pediatrics*; **12**(3): 538-553.

Onyedibe, K. I., Utoh-Nedosa, A. U., Okolo, M., Klo, O., Ita, O., Udoh, U. A., Nedosa, I. V., Bode-Thomas, F., Egah, D.Z. (2012). Impact of Socio-Economic Factors on Neonatal Sepsis in Jos, Nigeria. *Jos Journal of Medicine;* **6**: 2.

Osei-Safo, D., Egbo, H. A., Nattey, H., Konadu, D. Y., Addeamensah, I. (2016). Evaluation of the Quality of some Antibiotics Distributed in Accra and Lagos. *International Journal of Pharmaceutical Scenes and Research*; **7**: 1991-2000.

Otu, A., Elston, J., Nsutebu, E. (2015). Sepsis in Africa: Practical Steps to stem the Tide. *Pan African Medicinal Journal;* **21**; 323-6462.

Oyekale, O. T., Ojo, B. O., Olajide, A. T., Oyekale, O. I. (2022). Bacteriological Profile and Anti biogram of Blood Culture Isolates from Bloodstream Infections in a Rural Tertiary Hospital in Nigeria. *Africa Journal of Laboratory Medicine;* **11**(1): 2225-2010.

Pantell, R. H., Roberts, K. B., Adams, W. G., Dreyer, B. P., Kuppermann, N., O'Leary, S. T., Okechukwu, K., Woods, C. R. Jr., Subcommittee on Febrile Infants. (2021). Evaluation and Management of Well-Appearing Febrile Infants 8 to 60 Days Old. *Pediatrics*; **148**(2): e2021052228.

Parshuram, C. S., Duncan, H. P., Joffe, A. R., Farrell, C. A., Lacroix, J. R., Middaugh, K. L., Hutchison, J. S., Wensley, D., Blanchard, N., Beyene, J., Parkin, P. C. (2011). Multicentre Validation of the Bedside Paediatric Early Warning System Score: A Severity of Illness Score to Detect Evolving Critical Illness in Hospitalised Children. *Critical Care*; **15**(4): R184.

Patel, G. P., Balk, R. A. (2012). Systemic Steroids in Severe Sepsis and Septic Shock. *American Journal of Respiratory Critical Care Medicine*; **185**(2): 133-139.

Peterside, O., Pondei, K., Akinbami, F.O. (2015). Bacteriological Profile and Antibiotic Susceptibility Pattern of Neonatal Sepsis at a Teaching Hospital in Bayelsa State, Nigeria. *Tropical Medicine Health*; **43**(3): 183-190.

Pirozzi, N., Rejali, N., Brennan, M., Vohra, A., McGinley, T. (2016). Sepsis: Epidemiology, Pathophysiology, Classification, Biomarkers and Management. Herald Scholarly Open Access (HSOA). *Journal of Emergency Medicine Trauma Surgical Care*; **3**(1): 014.

Plunkett, A., Tong, J. (2015). Sepsis in Children. Clinical Review. *British medical Journal;* **3550**: h3017.

Polat, G., Ugan, R. A., Cadirci, E., Halici, Z. (2017). Sepsis and Septic Shock: Current Treatment Strategies and New Approaches. *Eurasian Journal of medicine*; **49**(1): 53-58.

Polin, R. A. (2012). Committee on Fetus and Newborn. Management of Neonates with Suspected or Proven Early-Onset Bacterial Sepsis. *Pediatrics*; **129**(5):1006-1015.

Prout, A. J., Talisa, V-B., Carcillo, J. A., Mayr F. B., Angus, D. C., Seymour, C. W., Chang, C. H., Yende, S. (2018). Children with Chronic Disease Bear the Highest Burden of Pediatric Sepsis. *Journal of Pediatric*; **199**: 194-199.

Puopolo, K. M., Benitz, W. E., Zaoutis, T. E., Committee on Fetus and Newborn; Committee on Infectious Diseases. (2018). Management of Neonates Born at ≥35 0/7 Weeks' Gestation with Suspected or Proven Early-Onset Bacterial Sepsis. *Pediatrics*; **142**(6): e20182894.

Raheemma, R. H., Qaddoori, B. H. (2021). Descriptive Study of Septicemia among Children under Five Years in Wasit Province, Iraq, in 2019. *Medico-legal update*; **21** (2): 719-722. https://ijop.net/index.php/mlu/article/view/2767.

Ramachandran, G. (2014). Gram Positive and Gram-Negative Bacteria Toxins in Sepsis: *A Brief Review Virulence*; **5** (1): 213-218.

Reinhart, K., Daniels, R., Machado, F. R. (2013). The Burden of Sepsis: A Cell Action in Support of World Sepsis Day 2013. *Special Article*; **25**(1): 3-5.

Rivers, E., Nguyen, B., Havstad, S., Ressler, J., Muzzin, A., Knoblich, B., Peterson, E., Tomlanovich, M. (2001). Early Goal-Directed Therapy Collaborative Group. Early Goal-Directed Therapy in the Treatment of Severe Sepsis and Septic Shock. *New England Journal of Medicine*; **345**(19): 1368 – 77.

Roca 1., Akova, M., Baquero, F., Carlet, J., Cavaleri, M., Coenen, S., Cohen, J., Findlay, D., Gyssens, I., Heuer, O.E., Kahlmeter, G., Kruse, H., Laxminarayan R., Liebana , E., Lopez-Cerero, L., Macgowan, A., Martins, M., Rodriguez-Bano, J., Rolain, J. M., Segovia, C., sigauque, B., Tacconelli E., Wellington, E., vila, J . (2015). The Global Threat of Antimicrobial Resistance: Science for Intervention. *New Microbes New Infection*; **6**:22-29.

Roland, D. (2012). Paediatric Early Warning Scores: Holy Grail and Achilles' Heel. *Archives of Disease in Childhood Education and Practice Edition*; **97**(6): 208-215.

Ronco, J. J., Fenwick, J. C., Tweeddale, M. G., Wiggs, B. R., Phang, P. T., Cooper, D. J., Cunningham, K. F., Russell, J. A., Walley, K. R. (1993). Identification of the Critical Oxygen Delivery for Anaerobic Metabolism in critically ill Septic and non-septic Humans. *Journal of the American Medical Association*; **270**(14): 1724-30.

Rubulotta, F. M., Ramsay, G., Parker, M. M., Dellinger, R. P., Levy, M. M., Poeze, M. (2009). Surviving Sepsis Campaign Steering Committee; European Society of Intensive Medicine; Society of Critical Care Medicine. An International Survey; Public Awareness and Perception of Sepsis. *Critical Care Medicine*; **37**(1): 167-170.

Rudd, K. E., Johnson, S. C., Agesa, K. M., Shackelford, K. A., Tsoi, D., Kievlan, D.R., Colombara, D. V., Ikuta, K. S., Kissoon, N., Finfer, S., Fleischmann-Struzer, C., Machado, F. R., Reinhart, K.K., Rowan, K., Seymour, C.W., Watson, R.S., West, T.E., Marinho, F., Hay, S. I., Lozano, R., Lopez, A. D., Augus, D. C., Murray, C. J. L., Naghavi, M. (2020). Global, Regional and National Sepsis Incidence and Mortality: Analysis for the Global Burden of Disease Study. *Lancet* **395**(10219): 200-211.

Ruth, A., Mc Cracken, C. E., Fortenberry, J. D. Hall, M., Simon, H. K., Hebbar, K. B. (2014). Pediatric Severe Sepsis: Current Trends and Outcomes from the Pediatric Health Information Systems Database. *Pediatric Critical Care Medicine*; **15**(19): 828-838.

Sands, K., Carvalho, M.J., Portal, E., Thomson, K., Dyer, C., Akpulu, C., Andrew, R., Feirreira, A., Gillespie, D., Hender, T., Hood, K., Mathias, J., Milton, R., Nieto, M.,

Taiyari, K., Chan, G. J., Bekele, D., Solomon, S., Basu, S., Chattopadhyay, P., Mukherjee, S., Iregbu, K., Modibbo, F., Uwaezuoke, S., Zahra, R., Shirazi, H., Muhammed, A., Mazarati, J.B., Rucogoza, A., Gaju, L., Mehtar, S., Bulanula, A. N. H., Whitelaw, A., Barnards Group And Walsh, T. R. (2021). Characterization of Antimicrobial Resistant Gram-Negative Bacteria that Cause Neonatal Sepsis in Seven Low and Middle-Income Countries. *Nature Microbiology*; **6**(4): 512-523.

Sangita, K. M., Tomar, R., Saha, N. K. (2019). Bacteriological Profile and Antibiogram of Blood Culture Isolate from a Tertiary Care Hospital. *International Journal of Medicinal Science Innovation Research*; **4**(6): 187-192.

Schwarz, N. G., Sarpong, N., Hunger, F., Marks, F., Acquah, S, E. K., Agyekum, A., Nkrumah, B., Loag, W., Hagen, R. M., Evans, J. A., Dekker, D., Fobil, J. N., Meyer, C. G; May, J; Sakordie, Y. A. (2010). Systemic Bacteremia in Children Presenting with Clinical *pneumonia* and the Impact of Non-Typhoid *Salmonella* (NTS). **10**(319).

Shane, A.L., Stoll, B. J. (2014). Neonatal sepsis: Progress towards Improved Outcome. *Journal of Infection*; **68**: 24-32.

Shankar-Hari, M., Phillips, G. S., Levy, M. L., Seymour, C. W., Liu, V. X., Deutschman, C. S., Angus, D. C., Rubenfeld, G. D., Singer, M., Sepsis Definitions Task Force. (2016). Developing a New Definition and Assessing New Clinical Criteria for Septic Shock: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *Journal of the American Medical Association*; **315**(8):775-787.

Sharma, D., Patel, R. P., Zaidi, S.T.R., Camerino, G.M., Aldo, B., Moras, L. A. (2017). Interplay of the Quality of Ciprofloxacin and Antibiotic Resistance in Developing Countries. *Frontiers in pharmacology*; **8**:56.

Shobowale, E.O., Ogunsola, F. T., Oduyebo, O. O., Ezeaka, V. I. (2016). Aetiology and Risk Factors for Neonatal Sepsis at the Lagos University Teaching Hospital, Idi-Araba, Lagos, Nigeria. *South African Journal of Child, Health*; **10**(3): 147-150.

Shobowale, E. O., Solarin, A. U., Faniran, A. A. (2017). Neonatal Sepsis in aNigerian Private Tertiary Hospital: Bacterial Isolates Risk Factors and Antibiotic Susceptibility Pattern. *Annals African Medicine*; **16**(2): 52-58.

Sisay, M., Worku, T., Edessa, D. (2019). Microbial Epidemiology and Antimicrobial Resistance Patterns of Wound Infection in Ethiopia: A Meta-Analysis of Laboratory Based Cross-Sectional Studies. *Biomedicine Central Pharmacology Toxicology*; **20**(35): 1-19.

Solomom, S. Akeju, O., Odumade, O.A., Ambachew, R., Gebreyohannes, Z., VanWickle, K., Abayneh, M., Metaferia, G., Carvalho, M. J., Thomson, K., Sands, K., Walsh, T. R., Milton, R., Goddard, F. G.B., Bekele, D., Chan, G.J. (2021). Prevalence and Risk Factors for Antimicrobial Resistance Among New Born with Gram-Negative Sepsis. *PLOS ONE;* **16**(8): e255410.

Souza, D. C., Brandao, M. B., Piva, J. P. (2018). From the International Pediatric Sepsis Conference 2005 to the Sepsis-3 Consensus. *Revista Brasileira De Terapis Intensive*; **30**(1): 1-5.

Souza, D.C., Barreira, E. R and Faria, L.S. (2017). The Epidemiology of Sepsis in Children. Review Article SHOCK; **47**(1), 2-5.

Sprung, C. L., Annane, D., Keh, D., Moreno, R., Singer, M., Freivogel, K., Weiss, Y. G., Benbenishty, J., Kalenka, A., Forst, H., Laterre, P.F., Reinhart, K., Cuthbertson, B.H., Payen, D., Briegel, J. (2008). CORTICUS Study Group. Hydrocortisone Therapy for Patients with Septic Shock. *New England Journal of Medicine*; **358**(2): 111-24.

Stoll, M. L., Rubin, L. G. (2004). Incidence of Occult Bacteremia among Highly Febrile

Young Children in the Era of the *Pneumococcal* Conjugate Vaccine: A Study from a Children's Hospital Emergency Department and Urgent Care Center. Archives of Pediatrics and Adolescent Medicine; **158**(7): 671-675.

Stormorken, A., Powel, K. R. (2011). Sepsis and Shock. 19th *Edition* Philadelphia: *Elsevier Saunders*;

Tan, J., Wang, Y., Gong, X., Li, J., Zhong, W., Shan, L., Lei, X., Zhang, Q., Zhou, Q., Zhao, Y., Chen, C., Zhang, Y. (2022). Antibiotic Resistance in Neonates in China 2012-2019: A Multicenter Study. *Journal of Microbiology, Immunology and Infection*; **55**(3): 454-462.

Tan, B., Wong, J. J., Sultana, R., Koh, J.C., Jit, M., Mok, Y. H., Lee, J.H. ( 2019). Global Case Fertility Rates in Pediatric Severe Sepsis and Septic Shock: A Systematic Review and Meta- Analysis. *Journal of American Medical Association of Pediatric*; **173**(4): 352-362.

Tessema, B., Lippman, N., Knupfer, M., Sack, U., Konig, B. (2021). Antibiotic Resistance Pattern of Bacterial Isolates from Neonatal Sepsis Patients at University Hospital of Leipzig, Germany. *Multi-disciplinary Digital Publishing Institute*; **10**(3): 323.

Thaver, D., Ali, S. A., Zaidi, A. K. (2009). Antimicrobial Resistance among Neonatal Pathogens in Developing Countries. *Pediatric Infectious Disease Journal*; **28**(1): S19-21.

Trippella, G., Galli, L., De Martino, M., Lisi, C., Chiappini, E. (2017). Procalcitonin Performance in Detecting Serious and Invasive Bacterial Infections in Children with Fever without Apparent Source: A Systematic Review and Meta-Analysis. *Expert Review of Anti-Infective Therapy*; **5**(11): 1041-1057.

Tsering, D. C., Chanchal, L., Pal, R., Kar, S. (2011). Bacteriological Profile of Septicemia and the Risk Factors in Neonates and Infants in Sikkim. *Journal of Global Infections Disease;* **3**: 42-45.

Utomo, M. T. (2010). Risk Factors of Neonatal Sepsis: A Preliminary Study in Dr. Soetomo Hospital. *Indones Journal of Tropical Infectious Disease*; **1**: 23.

Vandenberg, Q., Nyarukweba, D. Z., Ndeba, P. M., Hendrikson, R. S., Barzilay, E. J., Schirvel, C., Bisimwa, B. B., Collard, J. M., Aidara, K. A., Aarestrip, F. M. (2010) Microbiologic and clinical Features of *Salmonella species* Isolated from Bacteremic Children in Eastern Democratic Republic of Congo. *Journal of Pediatric Infectious Diseases*; **29**(6): 504-510.

Van Der Watering, M. D., Van Woensel, J. B., Lawrie, T. A. (2013). Prophylactic Antibiotics for Preventimg Gram-Positive Infections Associated with Long Term Central Venous Catheters in Ecology Patients' Cochrane Database Systematic Review; **11**: Cd003295.

Ventola, C. L. (2015). The Antibiotic Resistance Crisis Part 1: Causes and Threats. *Pharmacology and Therapeutics Journal*; **40**: 277-283.

Wang, H. E., Addis, D. R., Donnelly, J. P., Shapiro, N. I., Griffin, R. L., Safford, M. M. and Baddley, J. W. (2015). Discharge Diagnoses versus Medical Record Review in the Identification of Community-Acquired Sepsis. *Critical Care*; **19**(1): 42.

Wang, Y., Sun, B., Yue, H., Lin, X., Li, B., Yang, X., Shan, C., Fan, Y., Dong, M., Zhang, Y., Lin, W., Zuo, X., Su, P., Heng, Y., Xu, J. and Kissoon, N. (2014). An Epidemiologic Survey of Pediatric Sepsis in Regional Hospitals in China. *Pediatric Critical Care Medicine*; **15**(9): 814-820.

Watson, R. S., Carcillo, J. A., Linde-Zwirble, W. T., Clermont, G., Lidicker, J. and Angus, D. C. (2003). Epidemiology of Severe Sepsis in Children in the United States. *American Journal of Respiratory and Critical Care Medicine*; **167**(5): 695-701.

Weiss, S. L., Fitzgerald, J. C., Pappachan, J., Wheeler, D., Jaramillo-Bustamante, J. C., Salloo,

A., Singhi, S. C., Erickson, S., Roy, J. A., Bush, J. L., Nadkarni, V. M. and Thomas, N. J. (2015). Sepsis Prevalence, Outcomes and Therapies (SPROUT) Study Investigators and Pediatric Acute Lung Injury and Sepsis Investigation (PALISI) Network. Global Epidemiology of Pediatrics Severe Sepsis: The Sepsis Prevalence, Outcomes and Therapies Study. *American Journal of Respiratory and Critical Care medicine*; **191**(10): 1147-1157.

Weiss, S. L., Peters, M. J., Alhazzani, W., Agus, M. S. D., Flori, H. R., Inwald, D. P., Nadel, S., Schlapbach, L. J., Tasker, R. C., Argent, A. C., Brierley, J., Carcillo, J., Carrol, E. D., Carroll, C. L., Cheifetz, I. M., Choong, K., Cies, J. J., Cruz, A. T., De Luca, D., Deep, A., Faust, S. N., De Oliveira, C. F., Hall, M. W., Ishimine, P., Javouhey, E., Joosten, K. F. M., Joshi, P., Karam, O., Kneyber, M. C. J., Lemson, J., MacLaren, G., Mehta, N. M., Moller, M. H., Newth, C. J. L., Nguyen, T. C., Nishisaki, A., Nunnally, M. E., Parker, M. M., Paul, R. M., Randolph, A. G., Ranjit, S., Romer, L. H., Scott, H. F., Tume, L. N., Verger, J. T., Williams, E. A., Wolf, J., Wong, H. R., Zimmerman,

J. J., Kissoon, N. and Tissieres, P. (2020). Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction in Children. *Pediatric Critical Care Medicine*; **21**(2): e52-e106.

Wen, L. S., Oshiomogo, J. I., Eluwa, G. I., Steptoe, A. P., Sullivan, A. F. and Camargo, C. A. Jr. (2012) Characteristics and Capabilities of Emergency Departments in Abuja, Nigeria. *Emergency Medicine Journal*. **29**:798-801.

Wen, S. C. H., Ezure, Y., Rolley, L., Spurling, G., Lau, C. L., Riaz, S., Paterson, D. L. and Irwin, A. (2021). Gram-Negative Neonated Sepsis in Low- and Lower-Middle-Income Countries and WHO Empirical Antibiotic Recommendations: A Systematic Review and Meta-Analysis. *The Public Library of Science Medicine*; **18**(9): e1003787.

World Bank. (2016). During-Resistant Infections: A Threat to our Economics Future. Accessed on: 12 October 2022. https://www.worldbank.org/en/topic/health /publication /drug resistant-infection-a-threat-to-our-economic-future.

World Health Organization. (2014). Antimicrobial Resistance: Global Report on Surveillance. World Health Organization. Accessed on: 31 October 2022. https://apps.who.int/iris/handle/10665/112642.

World Health Organization. (2018). Global Antimicrobial Resistance Surveillance System (GLASS) Report. Early Implementation 2017-2018. 268: 9789241515061. Accessed:20 October 2022. https://www.who.int/publications/i/item/9789241515061.

World Health Organization (2020). Global Report on the Epidemiology and Burden of Sepsis. Current Evidence, Identifying Gaps and Future Directions; 978-92-4-001078- 9. https://www.who.int/publications-detail-redirect/9789240010789.

Wynn, J. L. (2016). Defining Neonatal Sepsis: *Current Opinion in Pediatrics*. 28 (2):135-140.

Zaidi, A. K., Huskins, W. C., Thaver, D., Bhutta, Z. A., Abbas, Z. and Goldmann, D. A. (2005).Hospital-acquired Neonatal Infections in Developing Countries. *Lancet*; **365**(9465):1175-1188.