Archives of Reproductive Medicine and Sexual Health

ISSN: 2639-1791

Volume 3, Issue 1, 2020, PP: 11-15

Investigating Neonatal Sepsis in Nigeria: Matters Arising

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Abstract

Neonatal deaths represents one of the greatest challenges to Nigeria's health outcomes, as MDG 4 of reducing infant deaths by two-thirds was one of the few goals the country failed to meet by 2015. Neonatal sepsis, bacterial infections present the bloodstream, accounts for 30% of all infant deaths in Nigeria. These infections are either spread via the birth canal or placenta during childbirth from mother to baby, or are nosocomial and a result of the environment. Most studies found a sepsis-positivity rate of around 20%, with the most common organisms being Staph Aureus, Coagulase-Negative Staph, Klebsiella and E.Coli.

Improved infection prevention and control measures must be implemented to decrease the prevalence of rare bacterial species in this setting. Isolation of 17 unique bacterial species causing and increased distance between sick patients are some ways that the high rates of infection and mortality can be combated. Clear guidelines for the prescription and administration of powerful antibiotics to these neonates must be implemented to slow the rapid rates of antibiotic resistance.

Keywords: *Neonatal; sepsis; bacteria factions; anitbiotic resistance; meropenem*

Introduction

Neonatal sepsis, the bloodstream bacterial infections acquired by babies in the first month of life, remains one of the main causes of death in infants in the developing world. Nigeria continues to suffer from one of the regions worst rates of infant mortality, with an average of 38.2 infant deaths per 1,000 live births [1].

Under five mortality rate in Nigeria is even higher, swinging between 56 deaths per 1,000 live births in urban areas and 87 deaths per 1,000 live births in rural areas [1]. Nigeria failed to meet the WHO's 4th Millennium Development Goal (MDG), which was aimed at reducing by two-thirds the under-5 mortality rate by 2015. 40% of deaths within this age group occur within the first 30 days of life, in a group classified as neonates [2]. One of the largest contributions to deaths in this age group is neonatal sepsis, which are bacterial infections in the bloodstreams of infants during the first month of life. Neonatal sepsis is responsible for around 750,000 annual deaths worldwide, with mortality rates being highest in the sub-Saharan Africa (SSA) region [3].

One of the driving causes for the difficulty in decreasing the amount of neonatal deaths attributed to bacteria sepsis is the growing issue of antibiotic resistance. The Center for Disease Control (CDC) has recently released a report outlining the severity of the issue or drug resistance, declaring the arrival of a "post-antibiotic era" [4]. Similarly, the United Nations estimates that drug resistant diseases will be responsible for a stunning 10 million global deaths per year by 2050 if serious interventions are not taken [5]. Rapid diagnosis and appropriate interventions are vital for the treatment of neonatal sepsis, but even with these measures in place drug-resistant bacteria can result in death. Multi-drug resistant bacteria has been attributed to over 30% of neonatal-sepsis deaths worldwide in 2016, and is expected to be steadily rising each year [5].

Neonatal sepsis is generally categorized into two categories based on the age of onset of symptoms related to sepsis such as fever, jaundice, respiratory distress, low heart rate, low blood sugar, and more. An infection acquired in the first three days of life

is classified as early onset neonatal sepsis (EONS) whereas an infection between the 4th to 28th day of life is considered late onset neonatal sepsis (LONS). EONS is generally associated with acquisition of pathogenic microorganisms acquired from the mother usually through transplacental spread or ascending from the cervix during childbirth. In contrast, LONS is typically the result of bacterial acquisition from the environment such as intravascular medical equipment and contaminated hospital surfaces [6]. Immunocompromised babies with issues such as pre-term births and low birthweights are believed to be at significantly larger risk for infection in the first month of life [7].

The Neonatal Sepsis Burden

Although neonatal sepsis is a global issue that significantly contributes to infant mortality in both developed and developing nations, patient outcomes are typically much worse in low-income areas. The increased danger of bacterial infections in the developing world is largely due to weak or failing healthcare systems, insufficient antibiotic access, poor sanitation and hygiene, and general resource limitations needed for adequate intervention. An estimated of 5.29–8.73 million disability-adjusted life years in the SSA region are attributed to neonatal sepsis, representing a majority of the global burden of disease for such infections [1]. An annual economic burden ranging from $10 billion to $469 billion dollars is estimated to be attributed to neonatal sepsis for this region [8]. These statistics paint a bleak picture of infant health in the SSA region and the scope of the issue is only amplified when considering the issue of drug resistance.

One important component of understanding the burden of neonatal sepsis infections is isolation and identification of bacteria responsible for infection. The three main categories of microorganisms that result in neonatal sepsis are gram positive bacteria, gram negative bacteria, and fungus. Within each of these categories are hundreds of species of different organisms with different biochemical characteristics, clinical manifestations, treatment options and pathogenicity. Every clinical setting has a unique makeup of organisms contributing to neonatal sepsis and can vary greatly depending on climate, population size, sanitation control, resource availability, rurality and other factors. In any investigation of neonatal sepsis, it is crucial to identify these organisms in as detailed a manner as possible so that appropriate treatment plans can be developed. Different antibiotics are given depending on the classification of bacteria present so accurate identification is crucial.

With an average mortality rate of 28% from neonatal sepsis, Nigeria is placed among the top five countries in the world with the most amount of newborn deaths [9]. The burden of neonatal sepsis in Nigeria is such that incidence of neonatal sepsis from 2011- 2015 ranged from 39.5-51.3/1000 live births. Thus, of the seven million annual births in Nigeria, according to 2013 census [10]; 276, 000 - 359, 100 children were estimated to have suffered neonatal sepsis.

Risk Factors Associated with Neonatal Sepsis

Neonatal sepsis is an infection that can occur to an infant in any setting but some certain factors have been associated for putting a child at increased risk of infection.

One of the most important factors strongly associated with sepsis is prematurity and low birth weight. Infants born pre-term generally have weaker immune systems, rendering them much more prone to infection. The APGAR score of the neonate, which quantifies infant health at one minute and five minutes after birth using factors such as appearance, pulse, grimace, activity, and respiration, has also been shown to be significantly associated with sepsis. There are also important maternal factors that pose increased risk for neonatal sepsis, including number of previous full-term pregnancies, mode of delivery, bleeding disorders, and premature rupture of the membrane [11].

Some physiological markers that are often considered to have a significant degree of predicative value for neonatal sepsis include c-reactive protein levels, white blood cell count, and lymphocyte count [12]. There are also ethnic and social factors associated with neonatal sepsis including poor or late prenatal care, low family socioeconomic status, poor maternal nutrition, and maternal substance abuse [11].

Common Pathogens associated with Neonatal Sepsis

Hundreds of various pathogenic bacteria has been shown to cause clinically significant infection in neonate and the identity of these bacteria vary greatly based on location. There are different common

pathogens responsible for sepsis in High-income countries (HIC) and low-middle income countries (LMIC). According to the WHO, the greatest burden of EONS in HIC is due to group B streptococcus (GBS) and Escherichia coli (E.Coli) [3]. LONS in these settings are most commonly caused by coagulase-negative staphylococcus (CONS). This in contrast to LMIC where the most common causes of sepsis in young infants are Staph. Aureus, E. Coli, and Kelbsiella spp. and in older infants Streptococcus pneumoniae (S. pneumoniae) and Klebsiella spp [3].

Route of Transmission for Pathogens causing Neonatal Sepsis

The process of how neonates acquire these pathogenic, deadly bacteria is also of utmost importance and must be considered. Suspected transmission routes for bacteria causing neonatal sepsis vary depending on the onset of infections. Bacteria causing EONS are usually based in the maternal genitourinary tract and go on to colonize the placenta, amniotic fluid, cervix, or vaginal canal. The infant may acquire such pathogen either intrapartum during the rupture of amniotic membranes or intrapartum, before the onset of labor.

The transmission of bacteria responsible for the onset of LONS is suspected to be very different than that of EONS [13]. Bacterial infections in the bloodstream of infants after the first 72 hours of life has been typically attributed to nosocomial sources such as health provider hands, mechanical ventilation, insertion of central lines, and total parenteral nutrition [14]. This life-saving equipment is commonly used in all NICUs for the purpose of improving the respiratory, dietary, and immune status of infants but can easily become colonized by bacteria.

Without strict guidelines on the disinfection of hospital equipment, a common issue in low-income areas, these devices can act a very serious threat to the health of immunocompromised infants. Central to the issue of reducing LONS is the proper disinfection during venipuncture, catheterization, and endotracheal intubation, as these are believed to be the leading source of such infections [14].

Clinical Treatment and lnterevention Analysis

Any study looking into antimicrobial resistance at a medical setting would be incomplete without analysis of how antibiotics are actually being given to patients. Irresponsible usage of antibiotics is a critical factor in the ongoing battle against growing resistance of life-saving antibiotics. The ways in which bacteria are developing resistance to these drugs is largely dependent on the ways antibiotics are being distributed and prescribed. In 2015, the WHO outline a "Global action plan on antimicrobial resistance" which contained 5 strategic objectives [3]. One of these objectives was to "optimize the use of antimicrobial medicines", as development of newer and more powerful drugs is useless if it is not combined with a behavior change in how antibiotics are being used.

One of the main mistakes contributing to this resistance is inappropriate usage of antibiotics in illness that are either not caused by pathogenic bacteria or not significant enough to warrant antibiotic usage. Less so of an issue in the developed world, inappropriate antibiotic usage is most prevalent in developing areas where drugs are sold without prescription and widely accessible without proper medical advice. Another large driver of resistance is failure to complete the full course of treatment, which happens all over the world. Treatment of neonatal sepsis at hospitals is done through intravenous (IV) or intramuscular (IM) antibiotics administration.

The most common antibiotics administered to neonates was Ampicillin and Gentamycin, which is correctly being prescribed as a combination recommended by the WHO [3]. Other most common prescribed antibiotics are Ciprofloxacin, a broad-spectrum antibiotic of the fluoroquinolone class that targets both gram-positive and gram-negative pathogens; Carbapenem Meropenem; Cephalosporin Ceftriaxone. However, a found abuse of Meropenem suggests the need for clinical review. Not only does inappropriate usage of antibiotics have serious long-term implications in the form of antimicrobial resistance, powerful drugs such as Meropenem can have immediate adverse side-effects on neonates and can cause death when used in cases where it is not absolutely necessary [15].

Antibiotics are very helpful in combating infection but, as is the case with any other drug, they come with adverse side-effects which may cause more harm to the patient than good. Recent studies have looked into the long-term side-effects associated with neonatal antibiotic use and have found compelling evidence showing that chronic issues such as asthma and obesity are strongly correlated with overusage of antibiotics early in life [16].

The theory behind such long-term implications of antibiotic usage is that every person is born with a microbiome composed of both harmful and incredibly important bacteria. Antibiotics are incredibly efficient at killing bacteria, but are not precise enough to only target pathogenic, harmful bacteria and so large amounts of benevolent bacteria are also destroyed, which can cause issues such as asthma and obesity. Over-prescribing antibiotics to neonates, contributing to the issue of microbial resistance as well as increasing the likelihood of long-term chronic illnesses in the patients [17].

Another important metric in assessing appropriate antibiotic usage is determining if antibiotics were prescribed in cases where bacterial presence was detected. As mentioned earlier, the usage of antibiotics for illnesses that are not caused by pathogenic bacteria is one of the driving forces of the threat of antimicrobial resistance. It is important to note one glaring limitation in most data is classifying a patient as "sepsis-negative" as there is a great likelihood that several of patients did have significant bacterial growth at the onset of symptoms but by the time blood samples is collected and tested, they had already received enough antibiotic treatment to kill enough bacteria and yield a false-negative.

One of the reasons that multi-drug resistance is considered such a dangerous threat is the belief that resistant bacteria will result in increased mortality due to difficulty in killing the pathogen. It is not impossible to come across situations where living patients had a greater average percent resistance to antibiotics than patients who died; where the range of resistance is actually higher in living patients than in patients who died. And where such difference is not large enough to reach statistical significance, further investigation is prompted. One possible explanation for such could be that resistance is not as immediate of a threat as rare and deadly pathogenic bacteria.

Multi-drug resistance cannot be tackled as a critical issue until basic infection prevention and control measures are implemented to prevent the spread of rare and deadly bacteria such as Pantoea. Simple and sustainable interventions like promotion of clean and timely deliveries, modern newborn care and specialized diagnostic facilities, hand washing and barrier nursing, and restriction of antibiotics may aid to reduce the burden of neonatal infection.

Justification for Action

Neonatal sepsis poses a substantial risk to infants receiving care at a NICUs in Nigeria where resources shortages are common, sanitation standards are often lacking, and antibiotic availability greatly varies [17]. Neonatal sepsis is responsible for almost 3 percent of total years of life lost and is ranked number eight in the top 25 causes for premature mortality in 2010, according to the Institute for Health Metrics and Evaluation [12]. Drug resistant microorganisms are known to lead to an increase in morbidity and mortality as they boost the risk of inappropriate therapy. On this background, data on the existence and prevalence of antimicrobial resistance is needed to define the best possible treatment for individual patients. More data and research on antimicrobial resistance is needed in order to provide recommendations on curbing antimicrobial resistance in Nigeria.

Knowledge on antimicrobial susceptibility patterns of the isolates are critical towards guiding empirical evidence, and combating AMR in Nigeria and beyond. Through the collection of neonatal blood samples, isolation and identification of bacterial isolates, screening for the antimicrobial susceptibility profile of first, second and third line antimicrobial agents, and determination of association between clinical features and sepsis, an improved understanding of the burden and way forward for treatment of neonatal sepsis at tertiary Hospitals can be developed.

Conclusion

Nigeria's failure to meet the 2015 Millennium Development Goal of reducing under-5 deaths by two third's is largely a result of limited progress in the death of infants in the first 30 days of life. Neonates represent a significant challenge for Nigeria and several other developing countries, as access to adequate medical technology and medications are pivotal to the survival of premature and immunosuppressed infants. Among other issues, bacterial septicemia is one of the main contributors to the ongoing mortality of neonates and an improved understanding of what is causing such sepsis and how to combat is imperative.

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Citation: **Uzoma K. Ndugbu.** *Investigating Neonatal Sepsis in Nigeria: Matters Arising. Archives of Reproductive Medicine and Sexual Health. 2020; 3(1): 11-15.*