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Neonatal Septicaemia in Poor Resource Settings

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Abstract

Neonatal septicaemia despite recent advances in hygiene and introduction of potent antibiotics has remained a major cause of morbidity and mortality worldwide. The developing countries worse as the incidence is as 56.9/1000 live birth in Nigeria. In our environment, the risk factors were low socioeconomic factors, delivery at home, maternal fever and use of traditional concoctions were the common finding and late presentation was another problem. In neonatal period, child immune defense mechanism is very low as the neonate whether term or preterm, have qualitative and quantitative deficiencies in cellular and humoral immunity compared to adults. When bacterial pathogens invade neonatal blood system, pro-inflammatory cytokines such as TNF-α, TNF-γ, interleukins a response followed rapidly by a surge of anti-inflammatory cytokines which include IL-10, IL-1RA, IL-13, IL-14, etc. Early presentation and prompt treatment with potent antibiotics improve the outcomes as most of those babies that presented early to our health facility and had treatment instituted early recovered well with no residual complication.

Conclusion: Therefore counselling and empowerment of mother of sick neonates play an important role in the mother to present such ill neonate whom may turn out to be a septicaemic neonate. This means early presentation to health facility, early diagnosis and early appropriate treatment thereby saving the neonate.

Keywords: Neonatal; Septicaemia; Pathogens and poor resource setting

Introduction

Neonatal septicaemia (NNS) may be defined as the clinical syndrome of bacteraemia with signs and symptoms of infection in the first twenty eight days after birth [1]. Some authors also define neonatal septicaemia as systemic bacterial infection in a neonate documented by positive blood culture within the first twenty eight days after birth [2,3]. Despite recent advances in hygiene such as scrupulous hand washing and introduction of potent antibiotics has remained a major cause of morbidity and mortality worldwide, with lesser magnitude in developed countries compared to developing countries [4]. With obligate observation of aseptic technique in the care of sick neonates and introduction of newer technology has further reduced the scourge of neonatal septicaemia in the developed countries however; same cannot be said in the developing world. This is because most of these newer equipment's are not available in these countries, and even the basic antenatal services are not readily accessible to the majority of expectant mothers in the developing countries, further worsening the high morbidities and mortalities [3,4]. The Very low birth weight (VLBW) [5,6] and the preterm babies who have poor or underdeveloped host-specific and non-specific protective mechanisms are most; affected by neonatal septicaemia [4]. The World Health Organization (WHO) estimates that about 1.6 million new-born babies die annually worldwide from neonatal septicaemia, with most of these deaths occurring in developing countries [4].

The epidemiology of neonatal septicaemia has been changing in patterns [5], the disease burden in North America and Europe has decreased [5] however, and the same cannot be said for the developing world. In most parts of Africa, and especially in Nigeria, the incidence of neonatal septicaemia has remained as high as 25-40% among neonates weighing 500-1000 g at birth and 12-14% among those weighing 1000-1500 g [7-9].

The pattern of bacterial aetiologic organisms, and the morbidity and mortality associated with neonatal septicaemia vary from place to place and from time to time. Neonatal septicaemia has remained a major cause of morbidity and mortality in the neonatal period and the burden of aetiologic organisms change from place to place and over time even in the same centre or region [1,3,6-8,10]. It is therefore important to maintain local vigilance so as to detect shifts in pattern early enough to intervene effectively. Infections are common problems of the new-born and children in developing countries [11]. Severe bacterial infections like septicaemia constitute a major cause of morbidity and mortality in the new-born accounting for 15 to 40% of neonatal morbidity [11,12]. It is one of the commonest causes of admissions into the neonatal intensive care units of developing countries [13].

Historical Background

In the 1930's, group A *β-haemolytic streptococci* was the most frequent cause of perinatal infections but it was controlled with

the introduction of the penicillin's [8,14]. The 1940's witnessed increased incidence of Gram-negative bacterial infection, particularly that due to *Escherichia coli* and the 1950s that of penicillinase producing *Staphylococcus aureus* which was controlled with more potent antibiotics [8]. The Gram-negative bacterial infection again became predominant in the 1960s, giving way to the group B *β-haemolytic streptococci* in the 1970s [8,14]. The group B *β-haemolytic streptococci* and enteric micro-organism have remained the most common infecting organisms in the United States in the delivery setting, while there is preponderance of Gram-negative organisms in the tropics [15-17]. In the 1980s, nosocomial infections became predominant in the intensive care nursery [14]. Rates of nosocomial infections were reported as high as 30 infections/100 patient discharges [14,18,19].

The risk of nosocomial infections is inversely proportional to the birth weight [5,6]. Very low birth weight (VLBW) and low birth weight (LBW) babies are at increased risk of nosocomial infections [5,6]. Intubation, indwelling catheters, parenteral nutrition, and antibiotic induced overgrowth of resistant flora increases the risk of nosocomial infections. Other contributing factors to nosocomial infections include lack of strict adherence to aseptic procedures, like scrupulous hand washing by neonatal intensive care unit personnel, and the presence of contaminated equipment and cleansing solutions [20].

Epidemiology of Neonatal Septicaemia

The incidence of neonatal septicaemia varies widely between the developed world and developing countries. It also varies from one nursery to another. The characteristic of neonates studied also influences the incidence. Thus, the prevalence rate is 3-10 folds higher in preterm than in full-term neonates [11]. Also, the incidence is higher in low birth weight (LBW) [5,6] than normal weight babies, and in males than females [13,21]. Other factors includes the levels of obstetric and nursery care available, the presence of predisposing factors like lack of good water supply, poor socioeconomic status, delivery at home or unhygienic environment [22]. A referral centre that caters for high risk and extremely low birth weight babies where survival is longer, the risk of repeated infections especially nosocomial infections is higher. Such a centre would have a higher incidence of neonatal sepsis than a hospital without such facilities and therefore does not admit high risk babies [23,24].

The reported incidence of neonatal septicaemia in developed countries such as Europe and North America ranged between 0.95/1000 live births and 3/1000 live birth [25,26]. This is similar to the reported incidence of 3/1000 live births report by Ayman et al. [27] from the United Arab Emirates (UAE). Another prospective study from Southern Israel reported an incidence of 2.5/1000 live births [28]. Recent report by Yoon et al. [29] from South Korea revealed an incidence of 1.05/1000 live births. This report is comparable to that of North America and European study. Earlier studies from Africa by Dawodu et al. from Ibadan reported that out of 7,626 neonates delivered during the study period, 70 had neonatal septicaemia giving an incidence of 9/1000 live births [22]. This result is higher than those reported from North America, Europe and the Middle East [25,27].

In another study done by Mokuolu et al. from Ilorin North Central Nigeria, 198 patients with suspected septicaemia were studied out of a population of 4,118 neonates. During the study 61 patients had septicaemia giving an incidence of 7.04/1000 live births [30]. In our prospective study from Maiduguri North-Eastern Nigeria out of 110 patient with presumptive diagnosis of neonatal septicaemia 46 patients had positive blood culture giving us incidence of 5.9/1000 live birth [31]. This report was lower than that of Mokuolu 2002 from Ilorin [31]. Amiebonomo from Zaria reported the incidence of 5/1000 live births [32] Airede et al. reported an incidence of 6.5/1000 live birth from Jos North Central Nigeria [33]. These results are higher than figures from North America, Europe and the Middle East. This may be explained by the fact that the developed countries have well equipped Hospitals with strong supportive laboratory, the mothers are well informed and know when and where to take their sick new-borns early enough to seek for care [26,27]. Although, these results were lower than the earlier report from Ibadan [22].

Report by Owa et al. from Ilesha of 17/1000 live births [34], Iroha et al. 17.09/1000 live births [35] and Njokanma et al. 35.02/1000 live births [36] from Sagamu, South Western Nigeria were higher than the report by Mokuolu from Ilorin, Ambe et al. from Maiduguri and that by Airede et al. from Jos. However this results were much higher than that by Ako-nai from Ile-Ife who reported the incidence of 5.5/1000 live births [37] The reason for the differences may partly be explained by the worsening economic situation of the country in the recent time so much that families live in poor housing condition and have difficulty in accessing good healthcare services.

Anah et al. (2006) from Calabar, South-South Nigeria reported an incidence of 54.9/1000 live birth [38]. This report is much higher than the earlier report from the same centre by Antia-Obong (1990) who reported an incidence of 19.3/1000 live births [39], The reasons given for this higher incidence were shortage of public water supply in Calabar metropolis and its environment, mothers presenting to their Hospital "only" when labour is complicated and generally poor utilization of available health care facilities among other reasons. Both reports are higher than those from Ibadan, Ile Ife and Lagos, South Western Nigeria [21,22,35-37].

Epidemiological data from developed countries show important differences not only in incidence but also in risk factors, bacteriological agents, as well as morbidity and mortality from that of developing countries. Group B *β-haemolytic streptococci* (GBS) and *Escherichia coli* are important causes of neonatal septicaemia between 2003-2005 in North America [40] and Europe [3,26]. However, in the tropics and subtropics, Gram-negative organisms are the predominant aetiologic agents, especially in the first week of life [3,41]. In a study from Bangladesh, Gram-negative organisms such as *Klebsiella spp*, *E. coli* were the predominant organisms causing neonatal septicaemia [42]. This reports was similar to that from Pakistan where *Klebsiella spp* was the predominant agents in 30%. A report from India, South East Asia, revealed the predominance of Gram-positive organism, *Staphylococcus aureus*, while *Klebsiella spp* predominated among the Gram-

negatives [43]. A study from Saudi Arabia showed coagulase negative *Staphylococcus aureus* (CONS) 24% as aetiologic organisms in neonatal septicaemia. Others included *Klebsiella spp* (12.9%) *Pseudomonas spp* and *Enterococcus spp* (11.3%) [44].

In study from the UAE, group B *β-haemolytic streptococci* were reported as the predominant aetiologic agents in NNS accounting for 24% [27]. These findings was in contrast with earlier report from Ibadan, Nigeria by Dawodu which revealed *Klebsiella spp* 46.6%, *Escherichia coli* 38.7%, while *Staphylococcus aureus* and *Staphylococcus epidemedis* 32% each [22].

A study by Ojukwu in Abakiliki South Eastern Nigeria reported Gram-positive organisms as the predominant with *Staphylococcus aureus* accounting for 45% while for Gram-negative, *Escherichia coli* accounted for 18.2% [3]. This report is similar to that by Anah in Calabar also South Eastern Nigeria, who reported Gram-positive as the predominant organism *Staphylococcus aureus* 53% while for Gram-negative *E.coli* accounts for 47% [38]. Report by Ako-nai in Ile-Ife reported Gram-positive *Streptococcus spp* as predominant in (45.3%) while *Klebsiella spp* in (54.7%) [38]. Ambe and colleagues in Maiduguri reported *Staphylococcus aureus* as the predominant organism (46.2%) and *Klebsiella spp* the predominant Gram-negative organism (24.8%) [31]. This agrees with the report by Mokuolu from Ilorin who isolated Gram-positive, *Staphylococcus aureus* as the predominant organism in (29.3%) of cases [30]. Studies have also documented a higher incidence of NNS in males than in females [22]. It is believed that females are doubly protected because of the protective gene, located on the X-chromosomes [22].

Neonatal septicaemia is higher in the preterm than term neonates because the preterm neonate's host defence, both specific (such as humoral and cellular) and non-specific (such as skin, mucous membrane) are poorly developed and not functioning optimally [22,45,46]. Neonatal septicaemia is divided into early and late onset. Early onset NNS is said to occur when the neonate manifests with the infection within the first 72 hours after. Early onset neonatal septicaemia is usually related to those organisms that colonize the maternal birth canal. This is further worsened by the mother's personal state of hygiene and low socioeconomic status [21,22]. The pathogens implicated in early onset neonatal septicaemia are predominantly Gram-negative enteric bacilli which include *Escherichia coli* and *Klebsiella pneumonia* [21]. The Gram-positive organisms that occasionally cause early onset neonatal septicaemia include GBS and *Staphylococcus aureus* [21].

Late onset neonatal septicaemia is related more too environmental factors and includes nosocomial transmitted infection. Affected new-borns suffer due to the fact that they stay longer on admission, and are at risk of repeated infections including nosocomial infections. Late onset neonatal septicaemia is environmentally related, meaning that it may or may not be related to antepartum or peripartum risk factors [21]. The categories of patients mostly affected include preterm/extreme, and very low birth weight neonate.

Risk Factors for Neonatal Septicaemia

The common risk factors for NNS in the developed world include prematurity and peripartum colonization of the birth canal by GBS [3,26]. In most of the studies from Nigeria, common risk factors included lack of good obstetric care, poor nursery practices, low socio economic status, poor housing conditions, poor personal hygiene, delivery at home/unhygienic environment, prematurity and complications of labour [3,22,29]. Most of which are preventable. The factors that influence the likelihood of neonatal infections can be classified into three groups; Maternal, Neonatal and Environmental [4,19,21].

Maternal Risk Factors

Breakage in the amniotic membrane either from trauma or iatrogenically prior to onset of labour, repeated vaginal examinations during labour play a significant role as risk factors for NNS [12,22]. Maternal low socioeconomic status, urinary tract infections (UTI), ante partum haemorrhage and maternal genital colonization by organisms like group B *Streptococcus*, *Escherichia coli*, *Listeria monocytogenes* lead to new-born infections [21]. Other conditions such as poor maternal nutrition, poor housing, overcrowding and inadequate/lack of ante-natal care which predisposes the pregnant mother to adverse conditions like anaemia, poor immune status are also risk factors for infections in the new-born. Such new-borns has little or no protection, because such mothers may not transfer enough protective antibodies in utero, and even after birth [4,19,21]. Maternal age less than 20 years and more than 30 years, nulliparity and maternal fever before, during or in the immediate postpartum periods, even in the absence of defined foci has been associated with increased risk of neonatal septicaemia [1].

Premature rupture of foetal membranes, greater than 24 hours, with symptoms and signs of chorioamnionitis has an increased risk for the exposed neonate to develop neonatal septicaemia. This increases further when manipulative obstetric procedures, are applied for assisted labour/delivery. Repeated examination *per vaginam* and forceps delivery both facilitate the invasion of amniotic membranes by microorganisms in the presence of poor maternal hygiene [4,21]. In our experience, maternal peripartum fever, antepartum haemorrhage, preeclampsia and eclampsia and delivery outside health facility or delivery at traditional birth attendance house and prolong rupture of amniotic membrane (PROM) were among maternal factors that closely corroborated well with developmental of neonatal septicaemia [31].

Neonatal Risk Factors

In a review of neonatal septicaemia between 1985-1988 in the United States, 3% of the episodes of septicaemia were early onset while 57% were late onset and mostly nosocomial infections. Early onset neonatal septicaemia was 25 times commoner in very low birth weight(1000 ≤ 1499 gms) or Extremely premature <32 weeks gestation than in term normal weight neonates [14] and mortality rate was higher (60%) in

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affected preterm infants than term infants (14%), poor host defence was responsible for increased susceptibility of the neonates especially the preterms [14]. Nosocomial infection was noticed to be 130 times more common in very low birth weight (VLBW) compared to normal weight infants with associated risk of 8.3% to 0% among the term infants. This shows that prematurity is the foremost risk factor for both early onset and late onset neonatal septicaemia because preterm neonates have even more significant deficiencies in immune competence than term neonates when compared to adults [14,19,21]. Poor cord care practices like use of cow dung, maclean (toothpaste), charcoal and warm rag application to umbilical stump were among neonatal risk factors for neonatal septicaemia in our settings [31].

The extremely preterm neonates also have weak skin barrier making it very easy for pathogens to cross the barrier. These infants also are often subjected to repeated invasive procedures, and prolonged hospital stay with the attendant exposure to antibiotic resistant hospital nosocomial flora. The frequent use of central venous and arterial catheters provide routes of entry for the microorganisms [19,21]. These neonates, especially the preterm who stay longer on admission in addition, experience prolonged endotracheal intubation or tracheostomy which provides direct access to the pulmonary mucosa while bypassing the innate cleansing mechanisms such as cough reflex and action of the cilia [21]. These inherent weaknesses in immune defence and immense exposure to high risk factors predispose them to develop septicaemia.

There is four-fold risk of infection in the male than the female. This is attributable to the single "X" chromosome which confers less resistance to male than females who have double "XX" [19,47,48]. The "X" chromosome has some genes that are responsible for the production of globulins which is responsible for curtailing infections. The presence of two normal representatives of the gene in the females and only one in the males explain the differences in vulnerability to infections [48]. It has been postulated that the first born of a set of twins is at higher risk for ascending infection than the second twin. This is due to the fact that during birth, the first twin sweeps the organisms colonizing the birth canal thereby taking a high inoculation of bacterial pathogens that might be present in the vagina [21]. Medications like steroids in the mother may lower her immunity thereby leading to development of opportunistic infection which invariably infects her new-born. Also use of broad spectrum antibiotics may increase the risk of infection by Antibiotic resistant strain of bacteria and invariably infecting her new-born [21]. The new-born with inborn errors of metabolism such as galactosaemia also has an increased risk of developing infection by Gram-negative organisms, particularly *Escherichia coli*. "However"; in developing countries there is paucity of reports of such finding which may be due to lack of facilities for making diagnosis [19,21]. Congenital defects resulting in interruption of the continuity of the skin or mucous membrane such as spina bifida; or an immune deficiency predispose to infections as well [21].

Of primary importance however, for preterm and term neonates there is need to adapt to extra uterine environment following delivery from essentially germ-free intra uterine environment. This transition process is met with challenge as neonates, whether term or preterm, have qualitative and quantitative deficiencies in cellular and humoral immunity compared to adults [19]. Maternal immunoglobulin G (IgG) crosses the placenta usually in the third trimesters, preterm neonates that are born before the end of the third trimester are deficient in this innate immunoglobulin. Immunoglobulin A (IgA) does not cross the placenta. It is barely detectable in cord blood at birth. Also, immunoglobulin M (IgM) does not cross the placental barrier. Synthesis of these immunoglobulins (IgM and IgA) by the foetus begins in the thirteenth week of gestation but occurs in small amounts [19].

In the new-born, both the classical and alternative pathways of the complement system have decreased activity compared to the adult. Complement activation is delayed, C3 and factor B are not produced in response to lipopolysaccharides challenge. The combination of deficiencies in the complement system and decreased total and specific antibodies together with decreased concentration of the fibronectin components results in major decrease in opsonization activity leading to increased risk to infections. Cellular deficiencies include depression in T^- and B^- lymphocytes and the natural killer (NK) cells functions [19].

Environmental Risk Factors

As the new-borns passes through the birth canal, they are exposed to maternal genitourinary microorganisms and to the flora in the nursery for those delivered in the hospital/admitted in the nursery units. Those delivered at home are exposed to microorganisms harboured by the attendant and those in the environment. In the nursery, colonization of the umbilical stump, the skin and the nasopharynx with the organisms in the nursery takes place within a few days, and within a few weeks the gastrointestinal tract is also colonized [19]. In the nursery environment where use of antibiotics is common, colonization of the neonate by resistant microorganisms is more likely even if the neonate is not on antibiotics. Occasionally, spread of infection within the nursery is aided by the personnel, most commonly by hand contact and contaminated equipment [19].

Neonatal Defence Mechanisms against Infection

The first level of defence against infection is at the skin and mucosal barriers. At the body surfaces and within the body cavities of an immune competent host are anatomic barriers and fluids that inhibits attachment and invasion by microorganisms [49,50]. In neonates, these barriers are innately weak and are further compromised by cutting the umbilical cord, setting up of intravenous lines for infusions, and breaking of the skin barrier for blood sample collection. This creates an easy access for bacteria to gain entrance into the neonatal host The next level of host defence is activated when microorganisms invade the body, in a non-specific response, circulating neutrophils confront the invading organisms and attempt to phagocytose them prior to lysis [17].

During lysis, Gram-positive bacteria release peptidoglycans whilst the Gram-negatives release lipopolysaccharides-A (LPS-A) or endotoxins. These substances initiate a cascade of events that lead to the sepsis syndrome, septic shock, multiple organ failure and death. Bacterial fragments, endotoxins and/or exotoxins stimulate monocytes and neutrophils to produce inflammatory mediators [17]. They activate complements, coagulation factors and the fibrinolytic cascades leading to the formation of vaso-active substances and the pro-inflammatory agents such as prostaglandins E, nitric oxide and platelet activation factor (PAF). Macrophages, cytokines such as tumour necrosis factor alpha (TNF-A), interleukins IL-1, IL-6, IL-8 and IL-10 have great influence in the progression of sepsis cascade [19].

Cells Involved in Host Defence

Phagocytes which includes monocytes, macrophages and polymorphonuclear (PMNs) cells phagocytosis the invading pathogens, antigens and cell debris thereby destroying them. To combat the invading microorganisms adequately the PMNS cells arrive at the site of invasion within a critical period of time (2-4 hours). Chemo taxis occurs due to factors released by the bacteria or from the complement system C5a. In the new-born, PMNs exhibit less chemo taxis than in the adult, which may be due to markedly decreased membrane deformability of new-born PMNs and deficiency of C3 and C5 [19].

Prior to phagocytosis, PMNs or macrophages attach themselves to the invading microorganisms. This is assisted by factors such as immunoglobulins, mainly IgM and complements, which include C3, C5 and C3PA, but these are reduced in the newborn. This may be due in part to decreased expression of the complement receptor CR3 (about 60% of the adult values) and a relative inability to generate free radicals Ca^{2+} ion, super oxide, hydroxyl radicals and hydrogen peroxide. The cationic proteins, lactoferin and lysosomal enzyme (myeloperoxidase) interact with hydrogen peroxide to form hypochloride ions which have bactericidal effect. The rate of this reaction in neonatal phagocytes is decreased because of poor production of hydroxyl radicals. All these essential functions are depressed further when an infant is stressed by infection.

Lymphocytes control the immune response, B-lymphocytes produce antibodies, while T-lymphocytes have multiple functions, including helping B-cells to make anti bodies, recognizing and destroying infected cells, activating phagocytes to destroy the pathogens, and controlling the level of the immune response. In the neonatal period however there is marked deficiency in number and function of lymphocytes [19].

Other Important Cells of the Immune System

Eosinophil's have a role in killing of parasites and controlling inflammation. Basophils, mast cells, and platelets release various inflammatory mediators which help accelerate the process of infection. Platelets produce platelet activating factor (PAF) which is responsible for the increased vascular permeability in severe neonatal septicaemia. Other cell types present antigens to lymphocytes which are processed for destruction and elimination from the body. Such interaction is to generate an effective immune response in an attempt to halt spread of infection, all of which are impaired in the new-born [19,21]. Humoral factors of host defence i.e. antibodies/ immunoglobulins, are produced by B-lymphocytes and plasma cells. In addition to the direct reaction with antigens, antibodies appear to play a significant role in the chemo taxis, phagocytosis and the release of mediators [19]. Immunoglobulin-M and Immunoglobulin-A does not cross the placenta and these do not appear in the term new-born in significant amounts. However, IgG is actively transported through the placenta from 30-32 weeks of gestation onwards, so that the term infant has an IgG level equal to or slightly greater than the maternal levels. Unfortunately not all classes of IgGs are transported equally across the placenta. Immunoglobulin-G2 and Immunoglobulin-G4 are transported in very small quantities. Preterm infants born before 30 weeks gestation are deficient in all classes of IgGs. Secretory IgA is present in colostrum and mature breast milk. It inhibits the adherence of bacteria to mucosal cell wall so; neonates that do not breast feed are deprived of the protective effect of IgA. Other immunoglobulin's included IgE and IgD but play little or no role in host immune defence mechanism.

Complements

The complement system has a major role in the defence against bacterial invasion and infection. It has two pathways, the classical pathway which is activated mainly by antigen-antibody complexes or aggregated immunoglobulins. The alternative (properdin) pathway is activated by endotoxins or complex polysaccharides [19,21]. There is no transfer of complement from mother to foetus. Term neonates have slightly diminished classical and significantly diminished alternative pathway levels. Complements C3, C4 and C5 are the most important functional components of the complement system and are approximately 50% of adult levels in term infant [21]. Much lower levels are seen in the preterm infants, leading to markedly reduced opsonizing capacity and increased risk of infections [19].

Cytokines

These are glycoproteins secreted by a variety of cells, particularly macrophages that act as self-regulating inflammatory mediators. Cytokines also modulate immune responses by acting as molecular messengers between cells. The production of interferons in the T-cells of new-borns is 10 times less than in adults. Tumour necrosis factor alpha (TNF-α) is also about 50% of the adult levels. These deficiencies, coupled with the reduced capacity to produce interleukins lead to reduced expression of adhesion molecules on both endothelial cells and phagocytic cells. Therefore, the sick neonates cannot curtail the spread of infection. The levels of TNF-alpha and IL-6 are increased in neonatal septicaemia which show the severity of inflammatory response in infections

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Pathogenesis of Neonatal Septicaemia

When a pathogen enters either the blood stream or any sterile body space/tissue, it is immediately recognized as "foreign" and is consumed by macrophages and other phagocytes, causing the organism to be lysed. This leads to the release of endotoxin (lipopolysaccharides from Gram-negative organisms and exotoxin peptidoglycans from Gram-positive organisms) leading to the simultaneous activation of the so called "sepsis" cascade. Activation of the macrophages stimulates the release of arachidonic acid metabolites like the prostaglandins and pro-inflammatory cytokines. This in turn leads to the release of anti-inflammatory cytokines and lipopolysaccharides further activating the complement and coagulation cascades. These events, working together or individually cause endothelial damage. In the healthy state, the human body maintain a balance between pro–inflammatory and anti-inflammatory cytokines.

However, this delicate balance is distorted by sepsis. Initially there is predominantly pro-inflammatory cytokines such as tumour necrosis factor alpha(TNF-α), tumour necrosis factor gamma(TNF-γ), interleukins(IL-1, IL-2, IL-6, IL-8), MCP-1, C4b-C3b a response followed rapidly by a counter balancing surge of anti-inflammatory cytokines which include IL-10, IL-1RA, IL-13, IL-14, Stnf-R, Sil-2R, tgF-beta. If the immunologic balance is regained, then the patient recovers, but if either the pro or the anti-inflammatory cytokines become predominant then the outcome is poor. As a consequence, systemic sepsis becomes a multisystem disorder with varying manifestations which include the cardiovascular system (CVS) manifesting as hypotension, shock. Haemopoietic manifestation may include neutropenia, anaemia and DIC. Septicaemia may lead to disability and death if metabolic effects and apoptosis are not checked in time [4,19,21].

Clinical Features of Septicaemia

The symptoms and signs of neonatal septicaemia are usually subtle and often non-specific. A high index of suspicion is therefore required on the part of the attending paediatrician for early diagnosis and prompt treatment [21,22]. By the time neonatal septicaemia is obvious to the inexperienced observer the disease is almost late [21]. Temperature instability such as hypo or hyperthermia i.e. temperature elevation of 38 °C point to bacterial infection [25]. A neonate with decreased mobility of extremities or swelling and erythema over a bone or joint may have osteomyelitis or osteoarthritis. Failure to thrive, sclerema and skin mottling are among the non-specific symptoms and signs of a septicaemia neonate [21]. Term neonate with septicaemia tends to have pyrexia while preterm neonate has hypothermia. Occasionally however, the neonate may appear well even though the patient is seriously ill [14]. The clinical features also depend on whether the neonate has early or late onset neonatal septicaemia, the presence or absence of local foci of infection. The symptoms and signs of neonatal septicaemia (NNS) mimic those of many other neonatal problems such as hypoglycaemia, asphyxia among other problems.

The neonate with septicaemia may present with symptoms of the respiratory system such as difficulty in breathing, apnoea, cyanosis, groaning, grunting, tachypnoea, intercostal and subcostal recessions. The clinical features we identified in our study were fever, irritability, jaundice, poor feeding, difficulty in breathing and lethargy, hyperpyrexia, abdominal distension and convulsions were the common manifestations [31]. The neonate may also present with gastrointestinal symptoms and signs such as poor sucking, vomiting, abdominal distension, diarrhoea, septic or foul smelling umbilical discharge and hepato-splenomegally usually in the late stages. Central nervous system symptoms and signs include convulsions or jitteriness, irritability, change in muscle tone (hypotonia or hypertonia) and abnormal reflexes. Symptoms and signs of haemopoetic system may include pallor, prolonged capillary refilling time, jaundice, petechial haemorrhages and bleeding tendencies.

Laboratory Diagnosis of Neonatal Septicaemia

The laboratory techniques used in the diagnosis of neonatal septicaemia can either be direct or indirect. Direct techniques are investigations that lead to the isolation of the offending microorganism by doing cultures of blood, urine, cerebrospinal fluid, gastric aspirate and aspirates or swabs from septic foci [43], while indirect techniques are investigations that provide indirect evidence of infections such as hematologic or immunologic parameters [43].

Direct Techniques for Diagnosis

Blood culture

The gold standard of diagnosis of septicaemia is a positive blood culture in the presence of clinical features and/or risk factors of septicaemia [3,14,38]. Blood samples collected for cultures must be adequate, usually 1-3 ml for both aerobic and anaerobic cultures, depending on the type of culture media [19]. Of the body fluids collected and cultured for NNS, it is observed that 52% of the pathogens were from blood culture, 25% from urine culture, 21% from cerebrospinal fluid and 15% from skin, eye or umbilical swab [51]. The different foci of infection from which organisms were cultured include meningitis, umbilical sepsis, eyes and skin infections. Most of the neonates had at least two of these combinations [22]. The common organisms we identified on blood culture include *Staphylococcus aureus* accounting for 69% of the Gram-positive isolates and *Escherichia coli* 39.2% of the Gram-negative isolates [31]. There were 12 cases of neonatal tetanus 5 of which had positive blood culture. Other organism isolated were *Staphylococcus epidermidis*, *Streptococcus pyogenes*, and *Streptococcus pneumoniae* while the other Gram-negative isolates were *Klebsiella pneumoniae, Haemophilus influenzae*, *Salmonella spp* and coliforms.

Buffy coat smear

Buffy coat smear employs examination of parts of supernatant of a centrifuged blood by microscope for presence

of bacteria in neonatal septicaemia [52]. It is a method of quick screening of neonate for bacteraemia/septicaemia [52]. Blood, about 1 ml is collected into an ethylene Diamine tetra acetic acid (EDTA) tube and centrifuged at 2500 rpm in a win Trobe tube for 15 min. The components after centrifuging are plasma, and the buffy coat with cells at the top of the tube. With the use of a pipette, the buffy coat is aspirated and three smears are made from it using the two slide technique. The smear is stained with Gram's stain and methylene blue. The stained field is scanned for at least 30 minutes before being considered negative. If organisms were seen the Gram stained slide is then inspected for identification and typing of the microorganisms for appropriate antibiotic use. Buffy coat smear screening method hastens the isolation of causative organism of NNS compared to blood culture which takes longer time [52]. The disadvantages associated with buffy coat smear includes: artefacts which may mimic microorganism on the poor slide preparation, it will also not tell whether the microorganisms are contaminants [52], and cannot be used for sensitivity of the organisms.

Cerebrospinal fluid culture

Examination of the cerebrospinal fluid in neonatal septicaemia is mandatory since meningeal involvement occurs in about 30% of affected neonates, and the choice and the duration of antimicrobial therapy is modified in the presence of meningitis [14,34]. Cerebrospinal fluid cell count, Gram stain, protein and glucose concentration should be assessed in addition to culture as the results when taken together confirm or exclude meningitis [14].

Urine culture

Urine culture is routine in cases of suspected neonatal septicaemia because the genitourinary tract may serve as a portal of entry for bacteria and/or depot for bacterial dissemination to the blood stream [19]. It has however, been suggested that urine culture is rarely positive in the first 72 hours of life except when there is a congenital urinary tract anomaly. The reason for this is unknown. Suprapubic bladder aspiration for urine collection is preferred to a clean catch and mid-stream collection in neonates [34,53]. In addition, cultures of other body fluids like umbilical and eye discharge, joint effusion are routinely done while investigating septicaemia [12,29].

Immunological Tests

Some ancillary investigations found useful in making early diagnosis of neonatal septicaemia include counter immune electrophoresis (CIE), latex agglutination and co-agglutination [14,21]. These are simple, rapid and accurate techniques for detecting bacterial antigens in body fluids, but they are not readily available especially in the developing countries because they are relatively expensive.

Indirect techniques

Results from blood cultures usually take up to 72 hours to become available, but some indirect techniques take minutes to a few hours. Thus, rapid indirect techniques help to substantiate diagnosis of suspected septicaemia early while awaiting the blood culture results. Available tests, though of differing sensitivities, may provide useful guide when used in combination. The most useful of these tests are the total and differential white cell counts [14]. Leukopenia of less than 5000 leucocytes/mm^3 in the first few days of life and 1000/mm^3 after a week of life; elevated immature to total neutrophil ratio (>16%) are likely to be associated with infection [14,21]. Other haematological indices of neonatal septicaemia include thrombocytopenia (<100,000/mm^3), blood film which may show toxic granulations and Dohle's inclusion bodies, raised erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). The use of the erythrocyte sedimentation rate as an aid in diagnosis of neonatal septicaemia is limited because of the large volume of blood required for this test using the classical win Trobe method. Due to this limitation a micro-method called mini-ESR using small volumes of blood has been developed [21]. The mini-ESR value has been found to have a high sensitivity and specificity as it can easily be done even in developing countries [55]. These tests may provide some guide when used in combination [21]. In our experience in the poor resource setting, absolute neutrophil count(ANC), immature to mature I/M neutrophil ratio>0.2, absolute platelet count (APC), erythrocyte sedimentation rate (ESR) were of great help in making early diagnosis of neonatal septicaemia as blood culture took several days before it became available [54].

Treatment of Neonatal Septicaemia

A high index of suspicion should be the watch word for diagnosing neonatal septicaemia. Clinical acumen is a major factor when making a decision on whether to commence treatment or not and when decision is made antibiotics should be commenced immediately as soon as samples are collected [19,21]. The management of neonates with septicaemia can be divided into general and specific measures.

General Measures

General measures are usually supportive therapies and include assisted ventilation, correction of fluid and electrolyte imbalance, pressor drugs and maintenance of a neutral thermal environment [14,32]. The use of exchange blood transfusion, transfusion of granulocytes, immunoglobulin and fibronectin as supportive management in neonatal septicaemia has been found to reduce morbidity and mortality. Blood transfusion as an adjunct to the antimicrobial therapy for severe neonatal septicaemia was widely used during the seventies. It was said to be associated with decreased mortality since bacterial endotoxins were removed in the process of exchange blood transfusion. Treatment was associated with improvement in the peripheral and pulmonary perfusion and enhancement of humoral and cellular immunity in the septicaemia neonate [21].

The use of granulocyte transfusion in the management of neonatal septicaemia is based on the association of neutropenia in septicaemia neonate with poor prognosis. The side effects of this treatment include graft versus host disease, transmission of

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hepatitis virus as well as the human immunodeficiency virus, and sensitization to leucocyte alloantigen's [21].

The administration of type-specific antibodies to neonate with septicaemia has been tried and seems beneficial to neonates with presumed group B *streptococcal* infection. However, the effectiveness in patients with established infection is uncertain, and whether intravenous immunoglobulin should be administered alone or in combination with granulocytes or other blood components (fibronectin) is yet to be decided [14,21].

Specific Therapy

The choice and administration of antibiotics for the treatment of infection is determined by the knowledge of local pathogens and their susceptibilities, the severity of the illness, and the policy of the unit based on the local epidemiology. McCracken and Eschenwald [25] recommended the use of penicillins (ampicillin or penicillin G) in combination with an aminoglycoside such as kanamycin or gentamycin [21]. Dawodu and Alausa in Ibadan [14,22]. Recommended the use of peicillinase resistant penicillin (cloxacillin or methicillin) in place of ampicillin and penicillin G, based on the bacteriology and sensitivity pattern they obtained in their study. In as recent study from Ilorin, Mokuolu and co-workers [30] recommended the initial empirical choice of ampicillin-sulbactam and aminoglycoside (Gentamycin) in their centre. In Maiduguri, Ambe and co-workers [31] recommended the use of second generation cephalosporins example cefuroxime and Gentamycin empirically. This may be changed whenever the sensitivity pattern result is obtained or when the patient does not respond to the initial antibiotic [21]. This initial empirical antibiotic cover may be changed as soon as the sensitivity pattern of the isolated bacteria is obtained and the most appropriate drugs is/are selected. Antibiotics are given for at least five to seven days in Gram-positive infections and ten to fourteen days in Gram-negative infection. However, when there is evidence of deep tissue involvement such as abscess formation, bone infection or meningitis, the antibiotic duration is extended to a minimum of twenty one days for meningitis and up to six weeks for bone infections [14]. In spite of timely diagnosis and appropriate treatment with appropriate antibiotics, the mortality and the associated squeal remain high in neonatal septicaemia [14,23]. The common empirical antibiotics that we use are the combination of second generation cephalosporins and aminoglycoside (Cefuroxime and Gentamycin), was based principally on our epidemiolocal studies and still works well for sick neonates, non-availability of other options and non-affordability of some of the higher potent antibiotics by the patients caregiver leave us with no other option, how in severe illness like meningitis we employ the use of Ceftriaxone and Gentamycin [31].

Prevention and Control

The prevention of neonatal septicaemia hinges on improved antenatal care, establishment of a program to deliver high risk mothers at medical centres with neonatal intensive care facilities and improvement of maternal socioeconomic status [14,21].

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