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EVIDENCE-BASED TREATMENT OF NEONATAL INFECTIONS IN DEVELOPING SETTINGS

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INTRODUCTION

Neonatal infections are major contributors to neonatal morbidity and mortality in the developing world. [1-3] Although, the incidence of sepsis is generally low, it may be associated with significant mortality. In some parts of the developed world, a prevalence of 6.6/1000 live births was reported, [4] and mortality associated with sepsis may be as high as 50% in untreated cases. [5] The prevalence of sepsis among Nigerian newborn babies was 22.9/1000 live births in Ile – Ife, 22.5/1000 live births in Sagamu and 7.98/1000 live births in Abakaliki. [6 - 8]

Neonatal sepsis is classified as **Early-onset** if features of sepsis develop within 48 hours of life. This usually results from perinatal exposure to microbes within the birth canal. [9] In **Late-onset** sepsis features begin to manifest after 48 hours of birth usually following environmental contamination either within the community (acquired from care givers) or within the hospital (acquired from the nursery staff and hospital equipments).

AETIOLOGY

In the developed world, 80% of severe neonatal infections are caused by Group B Streptococcus (GBS), Coagulase negative Staphylococcus (CONS) and Escherichia coli. The remaining 20% are due to infection with Pseudomonas aeruginosa, other Gram-negative bacilli (Klebsiella, Proteus, Enterobacter), Staphylococcus aureus and Listeria monocytogenes. [10]

In Sagamu, [2] Staphylococcus aureus, CONS, Klebsiella and unclassified Coliforms were the leading causes of neonatal sepsis. Similar patterns were reported in Ile-Ife and Abakaliki. [6, 8] Extensive literature search suggests that GBS is a rare cause of early-onset sepsis in the tropics including Nigeria. No case of GBS infection was reported among 127 babies screened for sepsis in Sagamu while only one case of GBS was identified among 138 babies in Abakaliki. [7, 8] Similarly, Listeria monocytogenes was not reported in these local studies. Although, Staphylococcus aureus was reported to be the commonest cause of all forms of neonatal sepsis in most Nigerian centres (35% in Sagamu, 36.2% in Ile-Ife, and 45.5% in Abakaliki), [2,6, 8] Gram-negative bacilli were mostly associated with early-onset sepsis.

RISK FACTORS FOR NEONATAL INFECTIONS

Risk factors for early-onset sepsis include maternal genital tract colonization with GBS, maternal urinary tract infection, maternal fever during labour, pre-labour rupture of foetal membranes for more than 18 hours, prolonged rupture of foetal membrane for more than 18 hours and chorioamnionitis. [11] Thus, the American Academy of Pediatrics [12] stipulated that routine screening of pregnant women with risk factors for GBS colonization (previous infant with GBS disease, GBS bacteriuria during pregnancy and preterm birth) should be done in the third trimester (between 35 and 37 weeks) to institute prenatal antibiotic therapy. Women with confirmed GBS colonization should have intrapartum penicillin to prevent GBS disease in the newborn. When GBS colonization is not confirmed, intrapartum penicillin should still be administered in the presence of intrapartum fever or prolonged rupture of foetal membranes. The former prevents 90% of potential neonatal GBS disease while the latter prevents about 69% of potential GBS cases. [12] Obviously, this protocol may not be applicable in this environment where GBS is reportedly rare.

Risk factors for late-onset sepsis include very low birth weight, prolonged hospitalization, invasive hospital procedures and prolonged broad-spectrum antibiotic therapy. [10]

CLINICAL FEATURES

Babies born with perinatal risk factors for sepsis may be symptomatic (called Probable Sepsis) or may be asymptomatic (Presumed Sepsis) at or soon

after birth. Most commonly, such babies are asymptomatic and may develop clinical evidences of sepsis rapidly. Sepsis is suspected in the presence of suggestive clinical or laboratory features which may warrant antibiotic therapy. It is proven or confirmed with positive bacteriological culture of blood, urine or cerebrospinal fluid.

Clinical features suggestive of sepsis include temperature instability, respiratory distress, vomiting, diarrhoea, poor feeding intestinal ileus, lethargy, irritability, seizures, abnormal muscle tone, loss of primitive reflexes, abnormal cry and poor skin colour. Suggestive laboratory evidences of sepsis include abnormal leucocytes count (low or high), left shift in differential leucocytes count, elevated band/neutrophil ratio, thrombocytopaenia and elevated C-Reactive protein.

MANAGEMENT

Antibiotics

There is a universal consensus on the need to manage infants with suspected or proven sepsis with broad spectrum antibiotics. It is recommended that newborn infants with suspected sepsis should have initial sepsis screen (blood culture, swabs culture) and parenteral antibiotics should be empirically commenced. Subsequent management depends on the clinical picture and the result of bacteriological screening. Nevertheless, the initial choice of antibiotics depends on the local prevalence pattern of organisms and pattern of local antibiotic resistance. For example, although, penicillin is the drug of choice for GBS but there are reports that the widespread practice of administering intrapartum penicillin for women colonized with GBS has led to increased risk of Methicillin-Resistant Staphylococcus aureus (MRSA).[13]

Traditionally, a combination of penicillin with aminoglycoside is used in the treatment of early-onset sepsis prior to the availability of bacteriological reports. Penicillin is meant to treat GBS and other Gram-positive organisms while the aminoglycoside is meant to treat coliforms. On the other hand, a combination of Flucloxacillin and Gentamicin is used to treat late-onset disease. These drugs treat Staphylococcus and coliforms. Flucloxacillin may be replaced with Vancomycin for Staphylococcus strains and Piperacillin for Pseudomonas. Due to widespread antibiotic resistance, the third-generation Cephalosporins are now to the rescue. Other aminoglycosides used in situations of resistance to Gentamicin include Tobramycin,Netilmicin,Amikacin and Kanamycin. However, the main concern about this class of drugs is the risk of nephrotoxicity and ototoxicity, particularly among preterm infants.

These recommendations do not show significant variation from the local findings on antibiotic sensitivity pattern of the aetiologies of neonatal sepsis. Gentamicin was recommended in Ile-Ife, Ilorin and Abakaliki, [6-8] but the overall sensitivity of 63 % of all the gram-negative organisms to Gentamicin in the Sagamu study indicated a declining trend in the sensitivity of these organisms to gentamicin. Remarkable resistance against the natural and synthetic Penicillins had been reported in most Nigerian centres, so, the combination of a second generation Cephalosporin (commonly Cefuroxime) and Gentamicin are used empirically for early-onset disease while Ceftriaxone with Gentamicin is used for late-onset disease.

These drugs are administered intravenously. Intramuscular administration is equally reliable and effective but carries the risk of muscle and nerve damage. However, there is no place for oral antibiotic use in neonatal sepsis except for urinary tract infections and superficial skin infections. For suspected sepsis, antibiotics must be administered until the bacteriological reports are available. However, the drugs can be stopped after 48 hours if the clinical signs improve and the blood culture reports are negative. If the blood culture reports are positive, the treatment must be tailored to the antibiotic sensitivity pattern of the isolate and must be continued for 10 to 14 days. When meningitis is present, the treatment may be continued for at least 21 days and for up to 4 weeks in the presence of osteo-articular infections.

It is important to monitor the plasma levels of aminoglycosides to avoid toxicity but this is not necessary with Cephalosporins and Penicillins. The plasma levels of aminoglycoside should be determined just before the next dose (trough) and 1-hour after the last dose (peak) to assess the efficacy of treatment and the risk of toxicity. The trough for Gentamicin should be <2µg/ml. When the trough is high, the dose frequency should be decreased to once in 36 hours or 48 hours to avoid toxicity and when it is low, the dose frequency should be

increased to once in 8 hours for better efficacy. Similarly, the peak for Gentamicin should be 6-10µg/ml. The dose must be reduced to avoid toxicity when the peak is high and when the peak is low, the dose must necessarily be increased for efficacy.[14-16]

Despite these developments and the various empirical modifications in treatment modalities, the mortality in neonatal sepsis remains significantly high in many parts of the world. Thus highlighting the need for improved and optimal antibiotic treatment of neonatal sepsis with the ultimate goal of reducing the morbidity and mortality associated with neonatal sepsis. This challenge has prompted several researches though with conflicting results. Therefore, systematic reviews of these randomized controlled studies which were carried out from the sixties till date were conducted to determine the statistical significance of the various findings in order to derive their clinical applicability.

These developments have not affected the global consensus that preterm infants with perinatal risk factors, irrespective of the absence of suggestive clinical features, should be commenced on empirical antibiotics until cultures are negative, in any way.[10]

Research Question: Should term asymptomatic babies with perinatal risk factors for sepsis be commenced on prophylactic or selective antibiotics?[17]

In randomized controlled trials of term asymptomatic babies whose mothers were screened for GBS colonization in pregnancy and term asymptomatic babies born to mothers with other risk factors for neonatal sepsis, the considered risk factors were intrapartum fever>/=38C, prelabour rupture of membrane>18hrs, prolonged rupture of membrane >18 hrs, chorioamnionitis, UTI detected during labour and confirmed genital colonization at 35-37 weeks of gestation without intrapartum antibiotic treatment.

Six eligible studies were identified in a systematic review but only two met the criteria for meta-analysis. Wolf[18] studied 49 babies whose mothers had prolonged rupture of membranes in Johannesburg, South Africa. Twenty four babies had penicillin and kanamycin immediately after birth and for 7 days while the remaining 25 did not receive prophylactic antibiotics unless they developed clinical evidences of sepsis. Gerard[19] also studied 67 babies whose mothers had confirmed GBS colonization between 32 and 34 weeks of gestation. Twenty-nine babies received prophylactic penicillin and sepsis screen while the remaining 38 were not put on antibiotic treatment but had similar sepsis screening. When sepsis was confirmed, antibiotics were commenced and administered for 7 days.

Gerard[19] reported that none of the babies developed sepsis and no mortality occurred. On the other hand, Wolf[18] reported that none of the babies on prophylactic treatment developed sepsis while 4 out of the 25 babies who did not receive antibiotic prophylaxis developed confirmed sepsis. Similar to Gerard's report, no mortality occurred.

There was no statistically significant evidence that prophylactic treatment prevents the development of sepsis since only 4 out of a total of 116 babies developed clinical evidences of sepsis. Similarly, there has been no sufficient evidence that even intrapartum antibiotic treatment of mothers with prolonged membrane rupture at term improves neonatal outcome.[20]

Research Question: Does combination antibiotic therapy have any benefit over antibiotic monotherapy in the treatment of neonatal sepsis?[21]

In randomized and quasi-randomized controlled studies comparing antibiotic regimens for the treatment of early neonatal sepsis, term and preterm newborns babies from birth to 48 hours of age requiring treatment for suspected neonatal sepsis were recruited. Although, 15 eligible studies were identified only 2 studies were reviewed. No study of antibiotic monotherapy versus monotherapy or combination antibiotic therapy versus combination antibiotic therapy was found. The 2 selected studies compared antibiotic monotherapy with combination antibiotic therapy.

Miall-Allen[22] compared Timentin (Ticarcillin and clavulanate) monotherapy with combination therapy of Piperacillin and Gentamicin among 72 babies while Snelling[23] compared Ceftazidime monotherapy with Benzylpenicillin and Gentamicin combination among 55 babies.

Although, Snelling[23] reported no mortality in both groups, Miall-Allen[22] reported 3 deaths in the

Timentin monotherapy group and 5 deaths in the Piperacillin and Gentamicin group. However, meta-analysis did not suggest a statistically significant difference in mortality in both groups. Similarly, Snelling [23] reported no case of treatment failure in both groups but Miall-Allen [22] reported 2 cases of treatment failure in the monotherapy group and 2 treatment failures in the combination therapy group. Meta-analysis did not show any statistically significant difference in the occurrence of treatment failures. Interestingly, none of the studies reported resistance of organisms to the antibiotics used.
Therefore, there is, as at present, no evidence that combination antibiotic therapies are more effective in the treatment of neonatal sepsis. It is also noteworthy that there are no recent similar randomized controlled trials. The aforementioned reviewed studies were done more than two decades ago and antibiotic resistance pattern could have changed remarkably in most neonatal settings since then. There are also no separate trials on antibiotic treatment of late-onset sepsis. Definitely, more randomized controlled trials are required to compare antibiotic monotherapies separately and various combination therapies separately.

Research Question: Do multiple gentamicin doses have any benefit over single gentamicin dose in the treatment of neonatal sepsis? [24]
In randomized and quasi-randomized controlled trials comparing a single dose per day and multiple doses per day regimen of Gentamicin in the treatment of neonatal sepsis, newborns with suspected or proven sepsis commenced on Gentamicin were studied. In all, 24 eligible trials were identified but only 11 (574 babies) were selected for review. All these were done between 1999 and 2004 in North America, India, Thailand, Germany, Spain and Australia. In all these studies, intravenous infusion of Gentamicin was used except one that used bolus over one minute. Two studies also used a combination of intravenous infusion and intramuscular Gentamicin. The dose used in all the studies was 4-5mg/kg/day either as single dose or multiple doses.

Although, meta-analysis did not show any significant difference in clinical efficacy (i.e clearance of proven sepsis) between the two groups, there was significant difference indicating that once-a-day regimen was associated with less failures of attainment of peak levels of at least 5ug/ml than multiple doses regimen. Similarly, there was a statistically significant difference indicating that once-a-day regimen is associated with less failures to achieve troughs levels of $\leq$ 2ug/ml than multiple doses a day regimen. These implied that there were no treatment failures in either the once-a-day or multiple doses a day regimen but there were significantly higher peak levels in the once-a-day regimen and significantly lower trough levels with once-a-day regimen. All these applied even when Gentamicin was given intramuscularly or intravenously.

Only one study reported hearing impairment in both groups of treatment but meta-analysis did not show any significant difference in both groups in terms of nephrotoxicity caused by Gentamicin.

In conclusion, although there was no difference in the clinical efficacy of the two Gentamicin dose regimen, the once-a-day regimen has many pharmacokinetic advantages over the multiple doses regimen thus making it safer for use. It is also noteworthy that preterms <32 weeks in both groups showed high trough levels probably because of lower GFR, hence, even once-a-day gentamicin dose may be toxic in these babies. Therefore, it is suggested that once in 36 hours or once in 48 hours gentamicin dose may be appropriate for this group of babies. [25,26]

Adjuvant therapies
Immunotherapy may be used to improve the survival of newborn infants who are also on antibiotic therapy. This may be in form of intravenous Immunoglobulin (IVIG) administration, Granulocytes transfusion or administration of Granulocyte-Colony Stimulating Factor (G-CSF) and Granulocyte-Macrophages Colony Stimulating Factor (GM-CSF). Maternal transport of immunoglobulin to the foetus occurs after 32 weeks of gestation and endogenous synthesis does not begin until 24 weeks after birth. Therefore, it is postulated that IVIG provides Immunoglobulin G which binds to cell surface receptors, provide opsonic activity, activate complements and promote antibody dependent cytotoxicity. [27] IVIG is used prophylactically (0.5g/kg weekly for 4 to 6 weeks) to prevent late-onset nosocomial infections in VLBW where it has been shown to significantly reduce sepsis but not mortality from sepsis. [28] It may also be used

therapeutically (0.5g/kg daily for four days) as an adjunct to antibiotics in all babies with suspected or proven sepsis.

Newborns have immature granulopoiesis and this predisposes to infections which in turn deplete the neutrophil storage pool in the bone marrow and neutropenia (defined as neutrophil count <1700/μL). The occurrence of neutropenia increases the risk of mortality in neonatal sepsis. [29] Thus, granulocyte transfusion prevents and treats sepsis-associated neutropenia and ultimately reduces the risk of mortality. These cells are prepared in concentrates form for transfusion either following leukophoresis or centrifugation of whole blood to yield buffy coat. The latter is easier and faster but it yields a lower dose of neutrophils compared to the former method. Therefore, buffy coat may appear to be less-effective in the reduction of mortality associated with sepsis than granulocytes concentrates prepared by leukophoresis. [30]

The G-CSF and GM-CSF are natural cytokines which boost the potent antibacterial functions of neutrophils and monocytes. They may be used prophylactically to prevent sepsis by stimulating neutrophil production and increasing the bactericidal actions of the neutrophils and monocytes in circulation. [31] These therapies appear to hold a lot of promise for the optimal prevention and treatment of neonatal sepsis.

Research Question: Does Intravenous Immunoglobulin reduce mortality in neonatal sepsis? [32]

Using randomized and quasi-randomized controlled trials involving newborns with suspected or proven infections, the effect of IVIG on mortality was assessed. A total of 9 studies (involving 553 babies) conducted in India, Mexico, Saudi Arabia, Switzerland, Taiwan, Turkey and US were selected. In all these IVIG was compared with placebo in babies with suspected or proven sepsis. For suspected sepsis, IVIG caused reduction in mortality with borderline statistical significance while it caused significant reduction in mortality in proven sepsis. IVIG use was also associated with significant reduction in duration of hospital stay for term babies but not for preterm babies. No adverse effect of IVIG was reported in all the studies. It was concluded that there is insufficient evidence (due to the small number of the babies studied) to prove that the use of IVIG should be routine in neonatal sepsis.

Research Question: Does Granulocyte transfusion reduce mortality in neonatal sepsis? [33]

Four small randomized controlled studies involving newborn infants with suspected or proven sepsis and neutropenia and were on antibiotics were selected for review. Three of the selected trials (44 babies) compared granulocytes transfusion with placebo while the last one (35 babies) used granulocyte transfusion versus IVIG.

The comparison of granulocyte transfusion with placebo revealed no significant difference in the mortality of both term and preterm with early or late onset sepsis. While there was no reduction in all-cause mortality when buffy coat transfusion is used, there was a reduction in all-cause mortality when leukophoresis-derived granulocytes were transfused. There was also no reduction in all-cause mortality when the dose of Granulocytes used was less than 0.5×10^9/kg or greater than 0.5×10^9/kg. However, there was a significant reduction in all-cause mortality with granulocyte transfusion compared with IVIG. Although no adverse effect of granulocyte transfusion (Graft-Versus-Host Disease) was reported in all the trials, the risk of transmission of infections like HIV, Hepatitis and Cytomegalovirus, though not negligible, may be significantly reduced with irradiation of blood prior to the harvest of granulocytes.

Due to the small number of babies studied, it is difficult to support or refute routine use of granulocytes transfusion in neonatal sepsis hence, larger randomized, controlled and blinded studies are required.

Research Question: Do G-CSF and GM-CSF prevent neonatal sepsis and reduce mortality in suspected or proven neonatal sepsis? [34]

Using 7 small treatment studies involving 332 babies, analysis of the use of G-CSF and GM-CSF was grouped into 3: treatment studies, prophylaxis studies and toxicity studies. Six studies used G-CSF for treatment while 5 studies used GM-CSF for both prophylaxis and treatment.

In the treatment studies, no significant reduction in mortality was reported babies treated between day 1 and 14 and between day 15 and 28. Indeed, only one

out of the 7 studies showed benefit from the use of CSF. GM-CSF was also shown to correct neutropenia within 48 hours of commencement in 3 of the 7 studies.

Only 3 studies reported prophylactic use of GM-CSF in babies <32weeks and < 1.5kg from birth and there was reduction in risk of sepsis in one group although the difference did not reach the level of statistical significance. However, one study reported complete prevention of neutropaenia among the babies till the age of 28 days. No adverse effect (oedema, bradycardia, anaemia, thrombocytopaenia, hyponatraemia) was reported in all the studies.

Prophylactic GM-CSF may protect against infection among babies <32 weeks who are neutropaenic or are at risk of developing neutropaenia but there is in sufficient evidence that G-CSF and GM-CSF in addition to antibiotics reduce mortality in preterms with suspected or proven sepsis. Indeed, none of the treatment studies demonstrated survival advantage by the age of 14 days.

Therefore, there is no conclusive or sufficient evidence that introduction of G-CSF or GM-CSF into clinical practice either as treatment of established systemic infection to reduce mortality or as prophylaxis to prevent systemic infection in high risk neonates is beneficial.

CONCLUSION

There is no controversy on the need to treat proven neonatal sepsis with antibiotics. However, the grey areas include the management of babies with presumed and suspected sepsis and the mode of antibiotic treatment of these conditions. The decision to use or not to use prophylactic antibiotics in babies with presumed sepsis should be individualized based on local peculiarities. Although, GBS is reportedly rare in Nigeria, other organisms especially Staphylococcus aureus, Escherichia coli and other Coliforms still constitute significant threat to newborn babies in the tropics.

While large pragmatic randomized controlled trials are awaited, the present local practice of empirical use of a Cephalosporin with Gentamicin in all babies with probable sepsis pending the availability of laboratory report may subsist. However, for term babies with presumed sepsis, basic sepsis screening (blood culture) and close observation for suggestive clinical features are adequate for 48 hours when laboratory report will be available. If clinical signs develop even before the availability of laboratory report, empirical antibiotics should be commenced and continued till the signs improve or the blood culture report is negative. Preterm infants with presumed sepsis should be commenced on prophylactic antibiotics once sepsis screening is completed.

Where they are available, adjuvant therapies, in form of Granulocytes transfusion, IVIG administration and CSF administration may be helpful in reducing the burden of neonatal sepsis in the developing world. Large randomized controlled studies are required to determine the best antibiotic regimen in the treatment of neonatal sepsis and establish the efficacy and safety of these adjuvant therapies in neonatal sepsis.

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