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REVIEW

Improving the Treatment of Neonatal Sepsis in Resource-Limited Settings: Gaps and Recommendations

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Abstract: Neonatal sepsis causes significant global morbidity and mortality, with the highest burden in resource-limited settings where 99% of neonatal deaths occur. There are multiple challenges to achieving successful treatment of neonates in this setting. Firstly, reliable and low-cost strategies for risk identification are urgently needed to facilitate treatment as early as possible. Improved laboratory capacity to allow identification of causative organisms would support antimicrobial stewardship. Antibiotic treatment is still hampered by availability, but also increasingly by antimicrobial resistance – making surveillance of organisms and judicious antibiotic use a priority. Finally, supportive care is key in the management of the neonate with sepsis and has been underrecognized as a priority in resource-limited settings. This includes fluid balance and nutritional support in the acute phase, and follow-up care in order to mitigate complications and optimise long-term outcomes. There is much more work to be done in identifying the holistic needs of neonates and their families to provide effective family-integrated interventions and complete the package of neonatal sepsis management in resource-limited settings.

Keywords: neonate, low- and middle-income countries, antimicrobial resistance, outcomes, sepsis

Introduction

Enabling children to thrive (rather than simply survive) has been highlighted as crucial global health targets by both the United Nations and the World Health Organization.[1,2] Neonatal sepsis remains a key barrier to this goal. It is an important cause of morbidity and mortality globally, with an estimated incidence of 6.31 million cases globally and 230,000 deaths in 2019.[3] This burden is disproportionately felt in resource-limited settings. The incidence of clinically suspected sepsis in low- and middle-income countries (LMICs) is estimated at 166 per 1000 live births and laboratory confirmed sepsis at 46.9 per 1000 live births,[4] with significant variation between individual countries and settings.[5] LMICs accounted for 93.91% of the world's total incident cases of and deaths from neonatal sepsis in 2019.[3] Although the burden of neonatal sepsis has decreased in high-income countries (HICs) over the last few decades, both incidence and resulting mortality have increased in LMICs.[6]

This high mortality burden in LMICs is mostly preventable, linked to persistent sociodemographic challenges such as poverty and lack of education for women,[7] and to health system challenges relating to both provision and utilisation of services posed by limited resources.[8] Inadequate access to care across the continuum from preconception, antenatal,[9] intrapartum,[10] to postnatal periods impacts the risk of sepsis and adverse consequences for vulnerable neonates.[11,12] For those who can access care, there is further risk due to suboptimal quality of care, lack of availability of antibiotics[13] and antimicrobial resistance.[14,15]

Researchers, clinicians, and policymakers have rightly focused on strategies to improve prevention, access to antibiotic treatment, and antimicrobial resistance, to combat neonatal sepsis in resource-limited settings. However, there has been less focus on developing a more holistic approach to managing neonatal sepsis in order to optimise

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outcomes. Providing supportive and family-integrated care during acute illness, and longer-term follow-up, is necessary to ensure that infants not only survive but subsequently "thrive";[16–18] these strategies should be integrated into the medical management of neonatal sepsis.

This review aims to summarise the key knowledge and implementation gaps in managing neonatal sepsis in resource-limited settings. Challenges surrounding diagnostics and antimicrobials will be discussed, but key research priorities will also be highlighted relating to supportive care, family-integrated care, and follow-up in this vulnerable population. We argue that a holistic approach is critical to reducing the unacceptably high morbidity and mortality from neonatal sepsis in resource-limited settings.

Background

Definitions and Aetiology

There is no consensus definition for neonatal sepsis. Common themes from the literature include isolation of an infective organism from blood or cerebrospinal fluid (CSF) samples, biochemical abnormalities such as raised C-reactive protein (CRP), and clinical features such as fever and apnoea.[19,20] Although the "gold standard" for diagnosis is a positive culture from either blood or CSF, most neonates treated for suspected sepsis have negative blood cultures.[21] This may reflect the level of caution used by neonatologists to commence treatment empirically, or the poor sensitivity of blood cultures when blood volumes of 0.5mL of blood or less are used.[22]

Neonatal sepsis is typically divided into early-onset disease (EOD) and late-onset disease (LOD). There is no clear consensus on the cutoff point between EOD and LOD, although many investigators and the UK's National Institute for Health and Care Excellence (NICE) consider EOD to be that which presents at 72 hours or before.[23–25] This distinction reflects the likely aetiology of the infection, with EOD resulting from vertical transmission of a pathogen from the mother at delivery or just prior, whether transplacental or ascending from the maternal genitourinary tract. LOD results either from vertical transmission, or horizontal transmission of a pathogen from the neonate's surrounding environment.[24] These two methods of transmission have obvious implications for prevention – reducing EOD depends on prevention and early treatment of maternal intrapartum infection, whereas reducing LOD depends more on infection control practices and management of indwelling devices in neonatal units.

Causative organisms vary according to geographical location and timing of infection. EOD is often caused by organisms that colonise the maternal genitourinary tract, with Group B Streptococcus (GBS) and Escherichia coli causing up to 70% of EOD in preterm infants in high-resource settings.[24] However, research from low- and middle-income countries highlights a potential difference in causative organisms, with *Klebsiella*, *Staphylococcus*, *Serratia*, and *Burkholderia* species dominating in one facility-based study.[4] Results may vary elsewhere with sampling methods and setting. For LOD, coagulase-negative staphylococci (CONS) are the main pathogens, causing up to 47.4% of disease in low- and middle-income countries.[26]

Clearly, strategies for reducing morbidity and mortality will differ between EOD and LOD due to their differing aetiologies, although some issues, such as antimicrobial resistance, are relevant to both. This review will primarily focus on EOD; EOD has an estimated 2.6 times higher incidence than LOD globally, and a higher mortality.[27] Additionally, some of the principal risk factors for LOD (such as mechanical ventilation, intravascular catheterisation, and surgery) are less relevant in a resource-limited setting where fewer neonates born at the extremes of prematurity survive and subsequently require prolonged and complex hospitalisations associated with LOD.[26]

Sequelae

Globally, severe infection is the direct cause of up to 26% of neonatal deaths.[28] Data on the short-term consequences of neonatal sepsis focus mainly on neonates who are born prematurely or at a low birthweight.[29] A meta-analysis found that neonates with sepsis who were born before 34 completed weeks' gestation and/or with birthweight ≤1500g, were almost twice as likely to die before hospital discharge (pooled relative risk 1.83, 95% CI 1.41–2.37) than those without sepsis. They were also statistically more likely to suffer adverse consequences including periventricular leukomalacia, intraventricular haemorrhage, and respiratory distress syndrome compared to neonates without sepsis.[29]

Survivors of neonatal sepsis are at high risk of adverse longer-term consequences. The negative effect on neurodevelopment is well recognised; infants who have survived neonatal sepsis are twice as likely to develop cerebral palsy, in addition to being more likely to have cognitive impairment, psychomotor delay, and visual and auditory impairment.[29,30] Whilst there is limited evidence of developmental outcomes following neonatal sepsis from LMICs, 39% of infants surviving neonatal meningitis in Jordan were found to have neurodevelopmental impairment, and 47.7% of very low birthweight infants in Brazil surviving sepsis.[31] Infants with neonatal sepsis are also at higher risk of impaired physical development, including reduced height, weight, and head size.[29,32]

Diagnostics

Rapid and accurate diagnostics are essential to improving the treatment of neonatal sepsis. These can be broadly divided into three categories: risk stratification and scoring to identify those at risk; microbiological testing to identify causative organisms and confirm a diagnosis; and biochemistry tests to monitor inflammation and response to treatment. All three approaches are core features of sepsis management in high-income countries, and all three must be improved to ensure adequate treatment in LMICs.

Risk Stratification

To maximise the chance of successful treatment, antibiotics for suspected neonatal sepsis should be initiated as soon as possible,[25,33] and so should not be delayed whilst awaiting biochemical or microbiological confirmation of the diagnosis. However, clinical signs of sepsis in the neonatal period are notoriously vague and often overlap with signs of other neonatal conditions or reflect the normal physiological process of transitioning to extrauterine life.[34,35] Therefore, timely identification of neonates at high risk of sepsis is essential, but also a major challenge. A variety of risk stratification and risk scoring systems exist primarily in HICs to facilitate the decision to start empirical antibiotic therapy after birth.[25,36] These consider maternal and perinatal risk factors for neonatal sepsis such as known GBS colonisation or intrapartum fever and may also include signs on clinical examination. These systems not only help to standardise the decision to initiate treatment but can also reduce antibiotic usage – by 75% in an American study.[37]

In resource-limited settings, clinicians lack an accurate and pragmatic risk stratification system. Few existing models have been developed or validated for use in LMICs, and those that have demonstrate high sensitivity but low specificity.[38] This can lead to unnecessary treatment, overburdening an already resource-constrained system; in such settings a more specific model to "rule out" sepsis is likely to be more useful. Additionally, existing models which have been adopted in high-resource settings often require relatively detailed information about the antenatal and perinatal history, such as maternal GBS colonisation status and gestation, which may not be available in settings with limited antenatal care provision.[39]

Microbiology

Identification of a causative organism of neonatal sepsis is a cornerstone of antimicrobial stewardship and allows clinicians to ensure a neonate has been adequately treated with the correct antibiotics.[35,40,41] The mainstay of microbiological diagnosis of neonatal sepsis is blood culture, with initial results usually in 36–48 hours depending on laboratory, although its sensitivity is affected by the small blood volumes sent in neonatal samples, and reliability dependent on adequate skin preparation to avoid contamination and false-positive results.[42,43] In resource-limited settings, the use of blood cultures is challenged by the prohibitive cost of consumables – such as blood culture bottles – and the longer transport time from patient to laboratory, particularly at high temperatures.[43–45]

Newer techniques are gaining traction in high-resource settings, such as molecular diagnostic platforms.[35,46] These techniques may be able to provide a more rapid diagnosis and require less labour time from laboratory staff.[43,47] However, the accuracy of these tests is not yet sufficient to entirely replace traditional culture methods,[46,48] and are at present too costly to be used in a resource-limited setting.[43,49] Many commercially available kits have too high a sensitivity leading to false positives where a contaminant has been detected, and do not yet provide any information on antimicrobial susceptibility.[43]

Biochemistry

Given the time required for diagnosis via culture, biochemical tests form an established part of neonatal sepsis management in high-resource settings. Biomarkers such as CRP and more recently, procalcitonin (PCT), are used as markers of inflammation to inform a diagnosis of neonatal sepsis and monitor response to treatment.[43] CRP, although non-specific, can be helpful in deciding the duration of antibiotic therapy with serial measurements and is relatively inexpensive.[43,50] Although biomarkers may provide additional data to aid clinical decision-making, they are not specific enough to be used independently to make or eliminate a diagnosis of sepsis.

Recommendations

The most important gaps in sepsis diagnostics to improve treatment are a lack of accurate risk stratification tools, and a lack of laboratory infrastructure. We recommend firstly that researchers develop and validate a new risk stratification model specifically for use in a resource-limited setting, with attention paid to the practicality of included risk factors so that the model can be used in routine clinical practice.

Secondly, investment in laboratory infrastructure and capacity building would have a sustained impact on the success of treatment of neonatal sepsis, also attracting research.[49] We believe that this investment should be focused on innovative "tropicalized" culture methods, such as using animals adapted to warm climates to produce agar,[51] and in laboratory staff training and retention, whilst reliable alternatives to culture methods become affordable for large-scale adoption in resource-limited settings. Improving the reliability of culture results using these new methods would improve understanding of local resistance patterns and facilitate decisions about antibiotic choices for empirical therapy. As clinicians gain confidence in the accuracy and utility of these blood culture results, increased demand for blood culture testing may help to drive down the price of a single test.

Antimicrobial Treatment

Treatment with antibiotics is the mainstay of neonatal sepsis management. Guidelines recommend intravenous or intramuscular treatment depending on the setting, for 36 hours to 7 days depending on the strength of suspicion of sepsis, with oral antibiotics rarely used in HICs.[25,52] The WHO recommends ampicillin (or penicillin) and gentamicin as first-line in hospital, which is in accordance with UK NICE guidelines, or oral amoxicillin where the suspicion of sepsis is lower, and families are unable to access hospital care.[25,52,53] All of these are classified as "Access" antibiotics according to the WHO's AWaRe scheme (a tool to support antimicrobial stewardship) and included in the Essential Medicines List.[54] However, the success of treatment hinges upon two factors, both of which can be problematic in the resource-limited setting: access and susceptibility.

Access to Antibiotics

Although consumption of antimicrobials has increased (by 36% between 2000 and 2010), many resource-limited settings still struggle with access to these critically important medicines, causing increased mortality and morbidity.[13] A study of 56 countries' antibiotic usage found significant variation,[55] although this was seen less for neonatal compared to paediatric sepsis.[56] The problem with antibiotic supply is no longer simply with access, but also with the appropriateness of prescriptions. The increase in consumption appears to be occurring primarily in LMICs with increasing economic growth, particularly where antibiotics are available for sale over-the-counter.[13] Previous studies have found significant antibiotic exposure in children in LMICs, but frequently with inappropriate prescriptions or choices; one study of eight LMICs found that the mean number of antibiotic prescriptions issued to children under 5 was 24.5.[57] The mean number of antibiotic prescriptions per child by age 5 in the USA is estimated at 8.21.[58] Access remains variable for newer antibiotics too – one study found that only 12 new chemical entities between 1999 and 2014 were sold in more than 10 countries.[59] It must also be remembered that the availability of an affordable antibiotic does not guarantee its quality – robust quality assurance and regulation are needed to ensure sufficient active ingredients to treat sepsis and avoid driving resistance.[13,60]

Antimicrobial Resistance

Resistance to currently available antibiotics has been increasing over many years and is now attracting the academic and policy attention it deserves. Neonatal sepsis is no exception, and it is impossible within the scope of this review to adequately describe all the factors contributing to its rise. Common causative organisms such as Klebsiella and E. coli have demonstrated resistance rates to first-line antibiotics of over 85% in South Asia and Africa,[61,62] and over 80% resistance to cephalosporins.[55,63] Unsurprisingly, this has a substantial impact on treatment success rates. Multidrug-resistant organisms are estimated to cause 30% of all deaths from neonatal sepsis.[13]

Neonatal antimicrobial resistance can be seen as a consequence of the relative lack of pharmacological knowledge in this population. Correct dosing and regimen duration are both key tools to ensure successful treatment of bacterial infection without the development of resistant species. Questions of "which dose" or "how long" may depend on the pathogen as well as the patient to balance side effects, intensity of selection pressure, and risk of undertreatment.[64] Although the knowledge base is improving, much of pharmacodynamic and pharmacokinetic understanding in neonates is still extrapolated from adult patients, with comparatively fewer studies available in neonates and significant inter-patient variability depending on gestational age and disease state.[65–67]

Interestingly, despite the unregulated availability of antibiotics "over-The-counter" in many resource-limited settings, some studies have found lower rates of antimicrobial resistance in community settings compared to hospitals.[68] This raises the possibility that oral antibiotic therapy could still be successful for mild illnesses, avoiding the need for broad-spectrum intravenous treatment and admission to hospital, even in areas with high resistance rates in the hospital setting. Clinicians should continue to use first-line, targeted antibiotics and community-based treatment where possible, to avoid patients contributing to, and being inoculated with, resistant pathogens in secondary care.

Data also suggest that antibiotics are in general overprescribed for the neonatal population; in South Asia, over 70% of possible serious bacterial infections in neonates did not have an identified cause, and almost half of those which had a cause identified were viral.[69] It is possible that many episodes of neonatal "infection" have a cause that is not bacterial, making the prescription of antibiotics for many of these episodes of presumed bacterial infection unnecessary. This practice represents a significant risk of increasing antimicrobial resistance, unless strategies for confirming bacterial pathogens are improved.

Recommendations

Antimicrobial resistance should be regularly reported, and these data collated by policymakers to inform appropriate regimens to healthcare workers in different settings. As part of this, dichotomies in resistance rates – such as that seen between community and hospital settings – should be verified, to allow the use of first-line antibiotics wherever possible and the reservation of second-line antibiotics for necessary cases only. Furthermore, the apparent overuse of antibiotics is likely to be a key factor driving antimicrobial resistance in neonatal sepsis and other infectious diseases and must be tackled as a matter of public health urgency.[68] This issue links back to the problem of diagnostics and risk stratification – without strengthening these systems, antibiotic use cannot be significantly reduced without risking the undertreatment of this vulnerable population.

Supportive Care

While antibiotics are the definitive treatment for neonatal sepsis, neonates should receive adequate supportive care, aiming to maintain physiological stability during their antibiotic therapy and recovery, to optimise their outcomes.[53] This may include respiratory, cardiovascular, and feeding support.[70] A meta-analysis found that neonates with sepsis are almost twice as likely to develop respiratory distress syndrome, almost 20 times more likely to develop multiple organ failure, and have almost double the mortality when compared to neonates without sepsis.[29] Although more intensive measures such as inotropic support[71] and even extracorporeal membrane oxygenation[72] may form part of this care in high-resource settings, we will focus on aspects applicable in the resource-limited setting: transfer to specialist hospitals, respiratory support, and nutrition.

Transfer

In resource-limited settings, a significant proportion of deliveries take place outside of a tertiary health facility, whether at home or in a smaller clinic or hospital. The prevalence of home births in LMICs is estimated to be 28%.[73] One study of Demographic and Health Surveys in 74 countries found that, in 13 countries, less than half of births took place in an institutional delivery service.[74] Non-institutional deliveries are more common among women who are poorer, less educated, or live in rural areas, and this inequality is increasing in many LMICs.[74] In some resource-limited settings such as Zimbabwe and Tanzania, there has been a very minimal increase in institutional delivery since 1990.[74]

When neonates are born at home or in smaller facilities and become unwell with sepsis, they require transfer to a more specialised facility to receive the appropriate care.[52] However, transfer to another facility often takes place via taxi, bus, or even motorcycle in resource-limited settings.[75,76] Journeys can also be very long – a mean time of 3 hours and 49 minutes was found in one South African study[77] – highlighting the need for improvements in safe transport strategies. Common consequences of these transfers are hypoglycaemia and hypothermia, which are associated with worse outcomes.[75,76,78,79]

Respiratory

Tachypnoea, apnoea, and other forms of respiratory distress are common signs of neonatal sepsis[70] and may require respiratory support to maintain oxygenation and ventilation. Hypoxia has been reported in up to 23.1% of sick neonates in LMICs,[80] and the resulting respiratory acidosis is linked to long-term adverse neurodevelopmental outcomes.[81]

In a high-resource setting, neonates unable to sustain sufficient ventilation or oxygenation are assisted by a range of respiratory support options from nasal cannula oxygen to high-frequency oscillatory ventilation, depending on the severity of their disease.[82,83] However, the more invasive interventions such as mechanical ventilation require costly equipment, reliable access to electricity, and close monitoring, generating a higher per-patient cost compared to older age groups.[84] They are therefore currently unavailable in many resource-limited settings, which is estimated to have a significant impact on neonatal mortality in these populations.[85]

Innovative alternatives to mechanical ventilation have been developed and successfully adopted in some resource-limited settings, such as bubble continuous positive airway pressure (bCPAP).[86] This provides continuous positive airway pressure via simple and inexpensive equipment and has been found to be safe for use in neonates.[86,87] However, many resource-limited settings utilise improvised bCPAP, which does not humidify or warm the air delivered to the infant, and lack adequate infrastructure relating to staff training, setup, and maintenance of equipment.[88,89] There is scarce evidence regarding the specific needs for respiratory support in resource-limited settings on which to base future innovations.[90]

Nutrition

Nutrition is essential for all neonates to survive, grow, and develop, and is of particular importance for neonates who are unwell (including those with sepsis). Pro-inflammatory cytokines cause protein catabolism during neonatal sepsis, as deaminated amino acids are used for gluconeogenesis to maintain glucose supply for the developing neonatal brain.[91] The severity of illness is associated with slower rates of growth and decreased fat-free mass, which are in turn associated with worse neurodevelopmental outcomes and future metabolic disease.[91]

Hypoglycaemia has also been found to be common in neonatal sepsis in a resource-limited setting, present in 32% of septic neonates in a study in India.[92] In Ethiopia, a study found that neonates with sepsis were three times more likely to be hypoglycaemic than those without sepsis.[93] This could relate to the increased metabolic demand during sepsis, but also to the poor feeding/ feed intolerance often seen in unwell neonates. Hypoglycaemia is also associated with higher mortality from sepsis when compared to normoglycaemic neonates.[92]

In a high-resource setting, nutritional support can be provided via enteral feeding with a nasogastric (NG) tube, intravenous (IV) fluids, or total parenteral nutrition (TPN) via a central venous line. TPN is usually unavailable in resource-limited settings,[94] and although many hospitals are able to provide intravenous fluids, many do not have fluid pumps or pre-mixed fluids, meaning the fluids must be prepared on the unit introducing a risk of infection.[12] Feeding practice in resource-limited settings is highly dependent on enteral feeding with maternal breastmilk, which is deemed to

be safe even for very low birthweight infants,[94] but there is little evidence to support specific practices to introduce or increase feeding in sick neonates,[95] and few centres have milk banks to support mothers unable to breastfeed or express milk.[12]

Recommendations

The main gap in the question of providing supportive treatments to neonates with sepsis is the lack of context-specific evidence. Little evidence exists as to how to improve the quality of neonatal transport, and although the issues of hypothermia and hypoglycaemia are well recognised, high-quality trials are needed to determine which interventions to mitigate these issues are most effective, and cost-effective.[78] In-utero transfer (before birth) is often preferable to postnatal transfer, if the mother is medically stable and delivery is not imminent.[96] This requires timely assessment and recognition of pregnancies at risk of neonatal complications, safe transport options, and robust links between health clinics, secondary and tertiary care, which are often lacking in resource limited settings. Prognostic scoring may help to allocate scarce resources to the highest-risk transfers.[79] Additionally, much more evidence is required about the nature of respiratory distress and hypoxia in septic neonates in resource-limited settings to quantify the need and allow development of innovative strategies to provide support, such as those not requiring external gas supply. More robust, randomised trials are also required to test the effectiveness of simple treatments for hypoglycaemia in the resource-limited setting, such as oral dextrose gel,[97] and to clarify optimal enteral feeding guidelines for feed intolerance in unwell neonates.

Family-Integrated Care

Family-integrated care (FICare) is a model of neonatal care which aims to integrate parents as core members of the caregiving team in the neonatal intensive care unit (NICU) and reduce some of the negative impacts of the NICU environment.[98] Painful, invasive procedures and separation from parents during the newborn period are linked with adverse neurodevelopmental and behavioural outcomes[98] – of which survivors of neonatal sepsis are already at higher risk. FICare has been found to promote family bonding, feeding, growth, parental well-being, shorter hospital stays, and improve neurodevelopment, in a variety of settings.[98,99] For example, introduction of FICare in one neonatal unit improved breastfeeding rates at discharge by over 10%, in addition to statistically significant improvements in daily weight gain.[100] There are multiple factors that can contribute to care being family-integrated within any neonatal unit, most relevant to neonates undergoing treatment for sepsis are the promotion of breastfeeding and kangaroo mother care (KMC).[99]

Breastfeeding

Breastfeeding has numerous positive impacts on the health and wellbeing of all neonates, including reduced overall and infection-related mortality.[101] The benefits extend into adulthood, with lower rates of obesity and type 2 diabetes compared to those who are not.[102] These benefits may relate to differences in the neonatal gut microbiota between exclusively breastfed and non-exclusively breastfed infants that have consistently been seen across different populations.[103]

Breastfeeding promotion is of particular relevance to neonates being treated for sepsis, because antibiotics have a significant and persistent impact on their microbiota, including reduced diversity, lower concentrations of protective species such as *Bacteroidetes*, and higher concentrations of *Enterobacteriacea*e.[104–107] Breastmilk plays an important role in the restoration of a healthy microbiota post-antibiotics; human milk oligosaccharides increase the levels of "healthy" bacteria such as *Bifidobacteria*, which in turn reduce gut permeability.[108] They may also reduce the growth of potentially pathogenic bacteria such as GBS.[108] Therefore, breastfeeding is a crucial intervention not only to support nutritional requirements and catch-up growth for the recovering neonate but crucially to minimise the harmful effects of antibiotic therapy.

Kangaroo Mother Care

KMC is a model of care designed specifically for preterm and low birthweight neonates, distinguishing it from FICare which is intended for all neonates, but has overlapping features and benefits. It warrants inclusion in this review due to its recommendation as an essential standard of care for all stable preterm/low birthweight babies (who are at increased risk of sepsis),[109] with research underway to assess the safety and impact in unstable babies.[110]

In the hospital setting, KMC involves skin-to-skin contact with the mother as much as possible (ideally at least 18 hours per day) and frequent breastfeeding (ideally exclusive).[99] Of all the parent-involved interactions studied in a meta-review, KMC was found to have the most consistent positive effect across infant and parental outcomes.[111] Skin-to-skin contact helps to regulate neonatal body temperature, particularly in cold environments or resource-limited settings without technology to keep neonates warm.[112] It may also improve respiratory and cardiovascular stability,[113] improve cerebral blood flow,[114] regulate stress,[115] and help relieve pain during clinical procedures.[116,117]

There are two aspects of KMC that are specifically beneficial to neonates being treated for sepsis, in addition to the generally positive effects it can have on any neonate living within the stressful and painful environment of the NICU. Firstly, KMC is associated with increased rates of successful breastfeeding[118] and reduced time to initiation of breastfeeding,[119] which can help to repair the microbiota after antibiotics as discussed above. Secondly, skin-to-skin contact is also associated with changes to the microbiota including a lower prevalence of organisms associated with gut dysfunction and other pathogenic species,[120] which may relate to the stress reduction and successful breastfeeding associated with skin-to-skin contact.[121] However, much of the research regarding the benefits of KMC focuses on preterm infants, and term babies are also at risk of neonatal sepsis, particularly in the resource-limited setting. Further research into changes in the microbiota and its associations with disease is required in order to make firm recommendations.[120] Finally, although contact with the mother seems preferable for infection control to handling by multiple healthcare workers or incubator sharing in resource-limited settings, particularly where neonatal wards may be crowded, further study is needed to ensure that skin-to-skin contact does not expose vulnerable neonates to pathogenic organisms.

Recommendations

There are clear, evidence-based benefits of family-integrated care models, including KMC. These benefits are both short term, such as improved establishment of breastfeeding and healthy microbiota, and longer term with improved growth and neurodevelopmental outcomes. However, much of the evidence for holistic, family-integrated initiatives comes from high-resource settings; more evidence is required to determine the most impactful, feasible, and acceptable interventions in the resource-limited setting. Additionally, given the differences in epidemiology of neonatal and childhood illnesses, more research is needed into the composition of neonates' microbiota in a resource-limited setting, and how this relates to health and disease.

Follow-Up

Follow-up care is a standard part of neonatal practice in high-resource settings.[122,123] Neonates born prematurely, with low birthweight, or who are significantly unwell during their neonatal period, are followed up with attention paid to growth, nutrition, and development.[124,125] Longitudinal surveillance with a healthcare professional enables early identification of issues and timely referral for interventions to improve outcomes for NICU graduates. This is relevant for survivors of neonatal sepsis due to the well-described impacts on physical and neurological development.[29,32] Finally, follow-up also presents an opportunity for health promotion by reviewing vaccination status and providing parental education on safe sleep and other essential health topics.[125]

Neurodevelopment

Neonatal sepsis is linked with adverse neurodevelopmental outcomes, including cognitive impairment and psychomotor delay.[29,30] It is recommended that at-risk neonates have regular neurodevelopmental assessments during their first 2 years of life,[125] to enable early intervention when they are not reaching developmental milestones. Hearing assessment should also form part of follow-up,[125] as prompt identification of hearing impairment and intervention (assistive devices, speech therapy) may improve outcomes.[126] Hearing impairment may also result from ototoxic antibiotic use, particularly where routine monitoring may not be possible.[127]

The evidence base regarding early neurodevelopmental interventions for neonates is growing,[128–132] but more research is needed, particularly in resource-limited settings, to determine which interventions should be prioritised for those identified to have developmental delay. Interventions focused on parenting skills and optimising the caregiving

environment have received increasing attention, and studies have shown promising results for improved infant and family outcomes.[133] At the population level, monitoring of neurodevelopment in neonates surviving sepsis will aid in planning for the provision of services to promote development and education.

Nutrition

Unwell neonates, including those with neonatal sepsis, may struggle to establish feeding and lose excessive weight during the newborn period due to both poor feeding and increased requirements. Follow-up care is a key opportunity to monitor longitudinal growth and offer nutritional interventions, and advise parents on optimal dietary choices and feeding strategies.[124] This is key for promoting long-term outcomes – early stunting is associated with reduced educational attainment, which can have a far-reaching effect on the child and their families' future.[134] Whilst breastfeeding is recommended where possible, more research is required to establish specifically which vitamins should be supplemented in growth-restricted or post-NICU infants.[135] Even nutritional interventions that are deemed useful in later infancy in resource-limited settings, such as vitamin A supplementation, have limited data to support their adoption in the neonatal period.[136]

Recommendations

Although follow-up care provides opportunities to monitor and intervene to improve development, nutrition, and parenting, more research is required in order to prioritise and plan follow-up services in a resource-limited setting. Firstly, without monitoring developmental and nutritional outcomes, it is difficult to anticipate the level of need among survivors of neonatal sepsis. It also remains to be seen which developmental interventions are most effective. Finally, follow-up clinic attendance is affected by multiple sociodemographic factors in resource-limited settings[137] – attention must be paid to ensuring services are accessible and equitable.

Multidisciplinary and Antenatal Considerations

Although this review has focused on the management of neonates with early-onset sepsis, it must also be recognised that prevention is far better than cure. Whilst the above strategies will help to improve mortality and morbidity from early-onset disease, prevention of sepsis begins during antenatal care – and even before. In the resource-limited setting, maternal and intrapartum factors such as hypertension and preterm labour were linked with increased risk of clinical and laboratory-confirmed sepsis.[4] Unsurprisingly, wider sociodemographic factors such as household income and rural residence also increased risk.[4] Tackling these issues is beyond the scope of this review, but the importance of multi-disciplinary collaboration between maternity, primary care, and public health cannot be overstated.

Conclusions

The current body of evidence on the management of neonatal sepsis is often focused on the timeliness and choice of antibiotic therapy; how best to diagnose neonatal sepsis, the likely causative organisms in that particular setting, and the optimal combination of antibiotics. However, as discussed in this paper, a holistic package of interventions accompanying antibiotic therapy is needed in order to ensure the septic neonate has the best possible chance of both "surviving and thriving". More research is required to determine which interventions and structures to support wider medical facilities, neurodevelopment, nutrition, and parenting, should be prioritized as health systems develop.

Abbreviations

LMIC, Low- and middle-income country; HIC, High-income country; CSF, Cerebrospinal fluid; CRP, C-reactive protein; EOD, Early-onset disease; LOD, Late-onset disease; NICE, National Institute for Health and Care Excellence; GBS, Group B Streptococcus; CONS, Coagulase-negative Staphylococci; PCT, Procalcitonin; RR, Relative risk; bCPAP, Bubble continuous positive airway pressure; NG, Nasogastric; IV, Intravenous; TPN, Total parenteral nutrition; FICare, Family-integrated care; KMC, Kangaroo mother care; NICU: Neonatal intensive care unit.

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