***Long-term impact of serious neonatal bacterial infections on neurodevelopment***

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***Abstract***

***Background:*** Neonatal bacterial infections have long been recognised as an important cause of acute morbidity and mortality, but long-term neurodevelopmental consequences have not been comprehensively described and discussed.

***Objectives:*** We aimed to summarise evidence on the pathogenesis, diagnosis, and epidemiology of long-term sequelae after neonatal bacterial sepsis and meningitis. We also discuss approaches for future studies to quantify the public health impact of neonatal infection-associated neurodevelopmental impairment.

***Sources:*** We identified studies, both research articles and reviews, which provide mechanistic information on long-term disease, as well as epidemiological studies that describe the frequency of neurodevelopmental impairment in children with and, for comparison, without a history of neonatal bacterial infection. Tools currently used in clinical practice and research settings to assess neurodevelopmental impairment were also reviewed.

***Content:*** We first enumerate potential direct and indirect mechanisms that can lead to brain injury following neonatal infections. We then discuss summary data, either frequencies or measures of association, from epidemiological studies. Risk factors that predict long-term outcomes are also described. Finally, we describe clinical approaches for identifying children with neurodevelopmental impairment and provide an overview of common diagnostic tools.

***Implications:*** The limited number of studies that describe the long-term consequences of neonatal infections, often undertaken in high income settings and using variable designs and diagnostic tools, are not sufficient to inform clinical practice and policy prioritisation. Multi-country studies with follow-up into adolescence, standardised diagnostic approaches, and local comparator groups are needed, especially from low and middle-income countries where incidence of neonatal sepsis is high.

**Epidemiology of neonatal sepsis and meningitis**

Neonatal invasive bacterial infections have high acute fatality risk, and can lead to long-term sequelae, despite adequate treatment (Figure 1). The two most clinically consequential presentations of neonatal bacterial infections are sepsis, which broadly corresponds to bloodstream infection with systemic inflammation, for which attempts have been made to establish consensus definitions (1,2), and meningitis, an infectious process involving the meninges and subarachnoid space. Globally, these conditions represent an important burden to children, with approximately 1.3 million cases of neonatal sepsis and other neonatal infections estimated to have occurred in 2017 and a large fraction of the 2.8 million all-age meningitis cases in 2016 occurring in neonates (3). A recent meta-analysis estimated the risk of neonatal sepsis as 28 per 1000 births, with a 3.5-fold higher risk in low-income compared to high-income countries (4). Incidences and relative frequencies of causative pathogens also depend on timing of infection, i.e., on whether the onset of symptoms occurs during the first days or week of life (early onset) or later during the neonatal period (late onset). In Table 1, we summarise different aspects of the epidemiology of neonatal sepsis and meningitis.

There are robust data on the acute severity of neonatal infections, with case fatality risks of sepsis and meningitis in low-middle-income countries (LMIC) of 18% and 40-58% respectively, and in high-income countries of 4% and 8% respectively (4–7). However, data on long-term outcomes of neonates who survive the acute infection are limited in quantity and geographical representation. In this narrative review, we describe evidence for the risk of neurodevelopmental impairment (NDI) after neonatal bacterial sepsis or meningitis. In particular, we discuss clinical studies providing mechanistic information on NDI associated with neonatal sepsis, as well as epidemiological studies that describe the frequency of NDI in children with and, for comparison, without a history of neonatal bacterial infection. Tools currently used in clinical practice and research settings to assess NDI were also reviewed. Finally, we discuss the consequences of increased NDI risk for clinical management of children and possible research directions.

**Pathogenesis of brain injury**

Brain injury in neonatal infections is best understood for meningitis, where there is direct infiltration of the central nervous system (CNS) by bacteria and subsequent inflammation. However, brain injury might result from neonatal sepsis without direct bacterial invasion of the CNS, evidenced by the associated increased risk of NDI (8,9).

Direct bacterial invasion of the CNS and cytotoxicity through activation of local inflammatory responses, are important mechanisms of brain injury in meningitis. Toll-like receptors (TLR) play an important role in the recognition of infectious pathogens and activation of pro-inflammatory responses, as well as increasing the risk of hypoxia-ischaemia, resulting in neuronal cell injury (10,11). In neonatal sepsis without meningitis, disruption of the blood brain barrier (BBB) by exposure to systemic bacterial cell wall components and inflammatory cytokines and entry of cytokines into the CNS resulting in inflammation and cytotoxicity have been described as a potential pathogenic mechanism (12,13). Cytokines have been locally identified in brain tissue and cerebrospinal fluid (CSF) of neonates with brain injury (14,15). Data from a study assessing levels of oxidative products in CSF of preterm infants with magnetic resonance imaging (MRI) evidence of brain injury support the role of cytokine induced oxidative damage in the pathogenesis (16). These and other direct and indirect mechanisms of brain injury in neonatal sepsis and meningitis are summarized in Table 2; including references (17,18).

The resulting injury is to the cerebral white matter and pre-myelinating oligodendrocytes, caused by inhibition of proliferation of neuronal precursor cells, activation of astrogliosis, stimulation of oligodendrocyte cell death and ultimately cystic periventricular leukomalacia (PVL) and non-cystic diffuse white matter injury (WMI)(19–21) . Consistent with this, infants with bacterial sepsis and meningitis are more likely to develop PVL compared to controls without sepsis (22,23). In addition, neonates with recurrent culture proven infections are at higher risk of progressive WMI (24). Preterm infants are particularly at risk, owing to the maturation dependent vulnerability of their developing brain. Other neurologic manifestations associated with foetal and neonatal infectious-inflammatory processes that can be detected on neuroimaging include intraventricular haemorrhage (IVH), cerebellar haemorrhage and reduction in cerebral growth and volume, which can all translate into poor neurodevelopmental outcomes (8,25).

**Bacterial sepsis and NDI**

Bacterial sepsis is often grouped as early or late-onset, culture-positive or culture-negative, by causative pathogen and whether it is a single or recurrent episode.

Both early and late-onset sepsis are associated with NDI. Early-onset sepsis has been associated with severe IVH and an increased relative risk of death or NDI at 2-years of age and cerebral palsy (CP) (26–28). Extreme preterm infants with bacteraemia at two to four weeks postnatal age were found to have increased risk of intellectual impairment at 10 years of age (29). A recent study in Denmark and the Netherlands compared NDI after confirmed Group B streptococcal (GBS) sepsis in the first three months of life to matched controls with no GBS disease. NDI was 1.5 to 2 times more common in survivors of GBS sepsis (30).

Many studies have reported on the association between sepsis and NDI based on whether it was culture-positive or culture-negative sepsis. In a multicentre cohort study of preterm infants <28 weeks, multivariate analysis showed that the odds of having CP in neonates with proven sepsis were increased three-fold when compared to culture-negative sepsis and those without sepsis (31). Although the odds of having NDI appear to be higher with culture-proven sepsis compared to culture-negative sepsis, the latter is much more common. In a study of late-onset culture negative sepsis affected infants had a higher risk for NDI compared to unaffected infants (9). In another prospective study of very low birth weight infants (VLBWI), 43% of infants with culture-negative sepsis had NDI at 18-22 months of age, compared to 29% in uninfected infants (8).

Studies have reported variable findings on the association between the type of bacteria causing sepsis and the degree of NDI. One study reported that Gram-positive sepsis was associated with a four-fold risk of CP, and a two-fold risk for NDI compared to no sepsis, while Gram-negative sepsis was not associated with NDI (31). Some studies have reported the opposite, with higher risk of NDI in sepsis due to Gram-negative pathogens (28,32,33). These differences are likely related to the design of studies, and confounders adjusted for. For example, high mortality related to Gram-negative sepsis may result in underestimation of its effect on NDI and potential differences in statistical power. Neurodevelopmental outcomes of neonates with multi-drug resistant (MDR) infections compared to those with susceptible infections is not well studied. A study done in Taiwan that analysed 376 Gram-negative bacteraemia episodes reported higher rates of neurological sequelae in MDR infections compared to non-MDR infections (34). Neonates with MDR infections have higher illness severity scores, higher rates of complications, prolonged duration of mechanical ventilation and prolonged hospital stay compared to neonates with non-MDR infections (35); these may relate to intrinsic features of the bacteria themselves, the types of babies affected, or the duration of time before receiving “appropriate” antibiotics. Some of these factors may themselves be associated with a risk of NDI and hence, studies assessing if MDR infections are an independent risk factor for NDI are warranted.

Recurrent infections during hospital stay in very preterm infants have been associated with poor motor outcomes (24,36). Most studies reporting on the association between NDI and neonatal sepsis are from high-income countries, with only few studies from LMIC (37), despite these countries having a high burden of neonatal sepsis. Two studies from Brazil reported that prevalence of adverse neurodevelopmental outcome was greater in VLBWI with sepsis than non-affected infants (38,39). One of these studies reported a 47% prevalence of cognitive impairment and 33.7% of neuromotor impairment at 12 months of assessment (38).

**Bacterial meningitis and NDI**

The risk of NDI after neonatal bacterial meningitis is higher than the corresponding risk after neonatal sepsis. Multiple studies have found that NDI is common in survivors of neonatal bacterial meningitis, with overall estimates ranging from one in three survivors for moderate to severe NDI to more than half for any NDI (40). High rates of developmental delay, cognitive, auditory, visual, speech and motor impairments, behavioural problems and neurological complications such as CP, hydrocephalus and seizure disorders have been reported. A meta-analysis of 8 published studies between 1989 and 2008 from the UK, Nigeria and America found point estimates of moderate or severe impairment in individual studies ranging from 16% to 38% (41). Two studies from the UK reported outcomes after 5 years from 172 of 280 patients who survived neonatal bacterial meningitis between 1985-87 (42), and 166 of 256 neonates who survived meningitis in 1996-97 (43). The authors found that despite a significant decline in acute phase mortality, serious long-term disability remained high; 26% in the 1986-87 cohort and 24% in the 1996-1997 cohort. In both studies combined, at 5 years, 9% of survivors were diagnosed with CP, 5% with epilepsy and 3% with sensorineural hearing loss. Eight percent in the first study were diagnosed with learning problems, and in the second study, 5% of survivors attended special schools and 20% attended a mainstream school with some form of additional support. A competing risk for studies assessing NDI is post-hospitalisation premature death. Although most children who do not survive neonatal bacterial meningitis die during the acute phase, death rates in survivors remain higher compared to controls (44). This may be explained by the increased risk of mortality secondary to associated long-term neurological impairments, though other risk-factors such as underlying co-morbidities may also play a role (45). In one study from the UK, 13 disabled patients of the 200 who survived the acute phase died before the age of five years (42).

Multiple studies studied predictors of poor outcomes in neonatal bacterial meningitis (46–48). CSF culture positivity has been observed as a predictor of long-term disability (43). Other predictors of death or NDI were seizures, abnormal neurological examination, need for inotropic support, low blood leukocyte count, low CSF glucose and high CSF protein, and abnormal brain imaging (46,48).

**Clinical spectrum of NDI and diagnostic tools**

Assessing NDI in survivors of neonatal sepsis or meningitis is important because early interventions can improve outcomes (49). Assessments may take the form of surveillance, screening, and specific/formative testing.

***Surveillance***

Surveillance is the process of ascertaining developmental delay at well baby visits, or at consultation with primary physicians or paediatricians (50–53). Assessments include obtaining a history noting concerns from the caregiver, milestone checks, and a neurological examination including assessment of hearing and vision. Surveillance is necessary for all neonates and children and more so for those with a history of sepsis or meningitis. Surveillance is not very sensitive and is often subjective (49).

***Screening***

The American Academy of Paediatrics (AAP), UK NICE and European guidelines recommend screening with validated tools at 9 months, 18 – 24 months and 30 -36 months (54–56). There are tests that can be administered in the neonatal unit before or at discharge. Some of the available screening tests which fall under the category of clinical assessments are shown in Table 3; including references (57–60). The listed screening tests are not exhaustive, but include ones that are more widely used.

***Specific/ formative testing***

If abnormalities are detected on surveillance or screening tests, specific testing should be conducted. These tests may be physician or parent administered. The most widely used physician administered tests are the Bayley Scale of Infant and Toddler Development (BSID-III) and the Griffiths Mental Development Scale (GMDS) (61). Trained personnel are essential to conduct these tests. The most commonly used parent administered test is the Ages and Stages III (ASQ 3) (62).

*Ages and Stages III*

The ASQ-3 is a parent administered test, which looks at 5 domains: fine motor, gross motor, communication, problem-solving and personal-social (62). In a study in the Netherlands the sensitivity of ASQ-3 to detect NDI was excellent (100%), its specificity was acceptable (76%), its negative predictive value (NPV) was 100% and there was a good correlation between ASQ-3 failures and NDI on the BSID III in the preterm cohort (63). The ASQ-3 has been used in 23 LMIC and translated into 16 languages (64).

*Bayley Scales of Infant and Toddler Development III*

The Bayley Mental Developmental Scale is regarded as the gold standard and may be administered up to 42 months of age. It has 5 scales which include the Cognitive Scale, Language Scale, Motor Scale, Social-Emotional Scale and Adaptive Behaviour Scale, all individually validated with a sensitivity between 93-98% and specificity between 95-98% (65,66).

*Griffith’s Mental Developmental Scale*

The GMDS has been used extensively in developmental paediatric research, with a well-documented cognitive validity (61). In a study on extremely low birth weight neonates a GMDS general quotient (GQ) score at 1 year had a low sensitivity of predicting low IQ at 5 years but a 3 year GQ score had a higher sensitivity (61). Other studies have shown a GQ score at 2 years to correlate better with NDI (67). In comparison with the Weschler Preschool and Primary Scale of Intelligence Revised (WPPSI – R), the GMDS may be a better measure of overall development but may not be very indicative of language development (68).

There are many other tests available for screening infants for NDI, as summarized in Table 4; including references (69–74). It is recommended to choose a test that is age specific, valid, reliable and has both cognitive and neuromotor subsets that will aid with longitudinal follow-up (Figure 2 and Figure 3). The tests used also depends on the resources available such as expertise, cost, time constraints and availability of tools to conduct the tests.

**Clinical consequences for follow up**

Quantifying the risks of NDI is important to allow appropriate counselling and follow-up of those at risk and to prioritise treatment and prevention strategies. Early identification of impairment and institution of appropriate interventions has been shown to improve outcomes of affected babies, including motor and cognitive outcomes, as well as hearing outcomes (75,76).

Knowledge of the NDI burden associated with sepsis and meningitis may justify consideration of new management strategies, including new antibiotics or adjunctive therapies, while identification of the burden associated with specific pathogens (such as *GBS, Klebsiella and E. coli*) may justify the investment needed for the development and implementation of novel maternal vaccines.

**Suggestions for future studies**

Box 1 summarizes the major methodological difficulties in interpreting results of studies conducted in this field. We strongly advocate for further studies and for the use of a standardised approach to their conduct. One possible study design is a prospective cohort study of survivors of neonatal infections, together with a comparator group and with multi-domain assessments (Box 2). Linkage of large databases is another approach that can be used for this purpose, as recently demonstrated (44). However, this approach also has methodological problems, including lack of standardised assessments as well as the likely inclusion of only those with severe NDI in these databases.

**Transparency declaration**

The authors declare that this narrative review was conducted in the absence of any commercial or financial relationships, activities or interests that could be construed as a potential conflict of interest. No external funding was received to conduct this review.

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All authors equally contributed to the conceptualization, literature review, writing, review and editing of the manuscript. RT is the lead and corresponding author, who in addition, lead the writing, integration and editing of the manuscript.

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