Neonatal Sepsis: Aetiology, Pathophysiology, Diagnostic Advances and Management Strategies

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ABSTRACT: Neonatal sepsis, a bloodstream infection in the first 28 days of life, is a leading cause of morbidity and mortality among infants in both developing and developed countries. Additionally, sepsis is distinguished in neonates by unique pathophysiological and presentational factors relating to its development in immature neonatal immune systems. This review focuses on the current understanding of the mechanics and implications of neonatal sepsis, providing a comprehensive overview of the epidemiology, aetiology, pathophysiology, major risk factors, signs and symptoms and recent consensus on the diagnosis and management of both early-onset and late-onset neonatal sepsis. It also includes a discussion on novel biomarkers and upcoming treatment strategies for the condition as well as the potential of COVID-19 infection to progress to sepsis in infants.

KEYWORDS: Neonatal sepsis, E Coli, Group B Streptococci, fungal sepsis, meningitis, procalcitonin, antibiotic resistance, intravenous immunoglobulin, Covid-19

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Introduction

Sepsis is a significant contributory factor of morbidity and mortality across all age groups; however, it is distinguished in neonates by unique pathophysiological and presentational factors attributable to the immaturity of their developing immune systems.[1]

Neonatal sepsis can broadly be described as a life-threatening, dysregulated inflammatory response to bloodstream infection in infants less than 28 days old.[2,3]

However, it is important to highlight the difference between early-onset neonatal sepsis (EOS), which occurs within 72 hours of life, and late-onset neonatal sepsis (LOS), which occurs after this 3-day period.[2,4] This classification helps explain some of the variation in aetiology, outcomes and treatments seen with neonatal sepsis.

This review will explore the epidemiology, aetiology, pathophysiology, risk factors, clinical features, diagnosis, management and complications of both LOS and EOS, taking into account historical and current/novel research findings.

Late diagnosis has always been a significant contributor to the challenges and complications associated with neonatal sepsis, and we will be exploring the large focus in current research on finding more sensitive biomarkers and faster diagnostic means to address this.[5,6] As the morbidity and mortality associated with this condition remain high and antibiotic resistance becomes a more pressing concern globally, efforts to standardise and improve prevention and management strategies are similarly a significant focus in this field and will also be discussed in this review.[6,7]

In writing this narrative review, we conducted an extensive search on PubMed/MEDLINE, EMBASE and ClinicalKey. Articles on both established knowledge and novel findings were screened on their relevance and applicability to the key topics being explored.

Epidemiology

The incidence of neonatal sepsis in the UK and other developed countries is estimated to be between 6 to 8 per 1000 live births.[8,9] In the United States, EOS incidence is up to 1 per 1000 live births, and, in 2016, the mortality rate for neonatal bacterial sepsis was approximately 14 per 100 000 live births.[10,11] With the global incidence, when taking into account low and middle-income countries (LMIC), being much higher, neonatal sepsis and other neonatal infections (NSNIs) accounted for nearly a quarter of a million deaths globally in 2016.[12]

Divergence between developed and developing countries also emerges when considering the trends regarding incidence, as while the global incidence of NSNIs has increased by about 13% from 1990 to 2019, countries with middle, middle-high and high socio-demographic indexes saw a decrease in incidence over this time period.[12,13] In 2016, the incidence of (culture-positive) sepsis seen in South Asian hospitals was 15.8 per 1000 live births, around 2 to 3 times the incidence reported in western countries.[14] This difference can partially be attributed to reduced EOS rates due to increased administration of intrapartum antibiotic prophylaxis against *Group B Streptococcus* (GBS) in richer countries.[15,16] Furthermore, the overwhelming majority of neonatal sepsis (99%) mortality occurs in LMICs,[17]

and in sub-Saharan Africa alone, an estimated 300,000 neonates die of sepsis annually.[18]

Positively, mortality rates associated with neonatal sepsis in both developed and developing countries have been decreasing, following from both generalised improvements in maternal and neonatal care as well as improved neonatal sepsis-specific knowledge and management strategies.[19,20] Nevertheless, sepsis still accounts for an estimated 15% of deaths in young infants.[13,21]

Aetiology

EOS is commonly due to vertical transmission by way of infection spreading to the neonate as they move through the vaginal canal during delivery or in-utero transmission via retrograde movement of pathogens from the vagina/cervix to the uterus and into the amniotic fluid.[22] As such, GBS, which is a common commensal coloniser of female genitourinary and gastrointestinal tracts, is often cited as the most common causative organism of EOS in developed countries.[23,24] *E. Coli* is another significant cause, implicated in between 10% and 35% percent of EOS cases and demonstrating a greater incidence in neonates with EOS than GBS in some studies.[23-25] *E. Coli* isolation rates are also concerningly rising among very low birth weight (VLBW) infants.[25] *Staphylococcus aureus, Listeria monocytogenes*, Coagulase-negative staphylococci (CoNS) and *Haemophilus influenzae* are other important, although less common, causes of EOS.[2,22-24,26] As a combination of an aminoglycoside (eg, gentamicin) and ampicillin or penicillin is used to treat EOS in most cases, information regarding sensitivity to these antibiotics among the most frequently isolated bacteria is important to monitor. Recent data from EOS cases in developed countries shows nearly all GBS isolates being sensitive to both ampicillin and penicillin.[25,27] While most E. Coli isolates are likely to be sensitive to gentamicin, there is a higher level of resistance seen in these isolates (10%) to standard cover.[25,27]

Conversely, LOS results from environmental exposure to infection after birth. This can be through transmission via healthcare workers, healthcare environments and other caregivers. In this case, CoNS like *Staphylococcus epidermidis* are the most common infection sources. *Enterobacteriaceae, Staphylococcus aureus* and *Candida* species are also relevant causes.[1,22,23,26,28] There is, however, contention regarding the proportion of cases where CoNs are contaminants rather than the sources of sepsis and how such instances may be assessed and differentiated.[24] CoNs are also often more resistant to standard antibiotic regimes than other isolated LOS pathogens and may require additional cover.[24,29]

Viral infections are a relatively rare cause of sepsis. However, in many instances, especially with Herpes Simplex Virus (HSV) infections, they can mimic symptoms of bacterial sepsis and should be considered in antibiotic-resistant sepsis.[30-32] In addition to vertically transmitted HSV, Cytomegalovirus (CMV) and other TORCH infections and enteroviruses are also among the viral agents implicated in sepsis or sepsis-like syndromes of the newborn.[33,34] CMV, for example, although itself a significant cause of congenital hearing loss and other neonatal morbidities, is also linked to and found in bacterial neonatal sepsis.[35,36] Both bacterial sepsis and CMV infection induce immune dysregulation that may lead to favourable conditions for the future or concurrent development of either infection.[34-37]

Fungal invasive candidiasis is a high-mortality, non-bacterial source of LOS with an increasing incidence in the 21st century. *Candida* is a coloniser present in around 30% of healthcare workers, and it's the third most common cause of LOS in VLBW infants.[38-40] The higher prevalence in this group may be linked to increased epithelial barrier translocation ability of pathogens in VLBW infants along with dexamethasone and antibiotic use promoting the growth of the virulent filamentous form of *Candida albicans*.[40,41]

Table 1 summarises and contrasts the major causative agents of both EOS and LOS in developed countries. It is important to note that in developing countries, where nosocomial infection is more common and seen earlier, gram-negative bacteria like *Klebsiella* and *E. Coli* are responsible for a large proportion of neonatal sepsis cases while GBS is less commonly seen.[42,43] It is important to note that there are significant regional differences in the aetiological makeup of neonatal sepsis, with 1 analysis of patients in sub-Saharan Africa finding the most frequent cause of EOS to be *Salmonella enterica* and *Acinetobacter* species and no cases attributable to GBS.[44]

Pathophysiology and Risk Factors

The way in which bacteria are able to breach immune defences and spread to the bloodstream is often linked to the unique characteristics and weaknesses of the developing immune system shortly after birth. The altered timeline of development for preterm babies also explains why they are at particular risk of initial infection and increased severity of infection.

The stratum corneum, which is the outer layer of the epidermis that forms the first barrier of innate immunity, does not gain full functionality until about 10 days after birth and this is extended several weeks in prematurity depending on the extent of early delivery.[45,46] Additionally, neonates born at less than 28 weeks of gestation lack adequate amounts of vernix, a biofilm produced in the third trimester that acts as an additional mechanical barrier until a few hours after birth. Vernix also provides antimicrobial peptides (AMPs) like lactoferrin and lysozyme.[47,48] The relative absence of vernix further serves to increase EOS risk in extremely preterm infants.

The largest amount of maternal igG antibody transference occurs in the third trimester, and premature delivery thus impacts the level of preformed antibodies available for neonates to access upon birth.[45,49] Furthermore, the relatively greater number of goblet cells in premature neonates increases the viscosity of respiratory secretions, which results in impaired

Table 1. Major causative pathogens of early-onset versus late-onset neonatal sepsis.[2,22-25].

EARLY-ONSET SEPSIS MAJOR PATHOGENS	FREQUENCY (%)	LATE-ONSET SEPSIS MAJOR PATHOGENS	FREQUENCY (%)
Group B Streptococcus	30-60	CoNS[a]	39-85
E. Coli	10-35	*Staphylococcus aureus*	5-18
Gram -Ve Bacteria excluding *E. Coli*[a]	7-30	*E. Coli*	5-13
Staphylococcus aureus	1-7	*Klebsiella* Species	4-9
CoNS	1-5	*Candida* Species	3-8
Listeria Monocytogenes	0-1	*Enterococcus* Species	6-15

Abbreviation: CoNS, coagulase negative staphylococci.
[a]In addition to E. Coli, gram-negative causes of neonatal sepsis include *Klebsiella, Pseudomonas, Serratia* and *Enterobacter* Species.

Table 2. Maternal, foetal and environmental risk factors predisposing the development of neonatal sepsis.[51-53,58,59]

MATERNAL FACTORS	FOETAL FACTORS	ENVIRONMENTAL FACTORS
Previous baby infected with invasive GBS	Prematurity (<37 wk)	Intravenous line insertion, mechanical ventilation
Chorioamnionitis	low APGAR score	Antibiotic use in neonate
Current maternal GBS colonisation, bacteriuria or active infection (UTI)	Inability to breastfeed	Frequent blood sampling
Rupture of membranes >18 h (higher association if >24 h) before labour onset	Low birth weight	Unsanitary handling of baby and umbilical cord
Multiple vaginal examinations	Meconium-stained amniotic fluid	

mucociliary clearance, while surfactant proteins that play important roles in respiratory mucosal defence are also reduced in this group.[50,51] Ruptured membranes >18 hours, chorioamnionitis/intra-amniotic infection and maternal infection (Most commonly UTIs followed by vulvovaginitis) during pregnancy are other key risk factors to consider.[52-54] Not only is there a risk of vertical transmission (eg, through foetal ingestion/inhalation of amniotic fluid) in these conditions, but there is also some evidence to suggest that maternal infection may cause hypermethylation (and, therefore, decreased expression) of genes involved in foetal immune development.[55-57] Clinically important maternal, foetal and environmental factors linked with neonatal sepsis are highlighted in Table 2.[51-53]

Risk for LOS is often similarly increased by the immaturity of the neonatal immune system; however, interventions like central venous catheter and intravenous line insertion present additional pathogen entry mechanisms.[60] Furthermore, antibiotic use and hypoxia potentiate intestinal mucosal injury and microflora disruption. This is particularly relevant in neonates, where specialised innate immune cells within the intestines produce interleukin-17 (IL-17), a cytokine that plays an important role in both infection prevention/removal and the exaggerated immune responses seen in the pathogenesis of sepsis.[61-64]

Sepsis, in both adults and neonates, can be characterised as an inadequate local immune containment response to infection that provokes dysregulated systemic immune activity, leading to systemic inflammatory response syndrome (SIRS).[65] Once physical barriers have been breached, the interaction of Bacterial Lipopolysaccharide (LPS – a Pathogen Associated Molecular Pattern (PAMP) molecule) with Toll-like receptor 4 (a Pattern Recognition Receptor on myeloid cells) is a significant instigator of a pro-inflammatory cascade that upregulates the production of cytokines like tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6).[66] While these inflammatory mediators are beneficial and indeed vital for pathogen removal in the presence of small amounts of LPS, larger amounts of this endotoxin can impair the coordination and regulation of the immune response and lead to out-of-proportion vasoactive changes.[67] A similar mechanism occurs with other causative pathogens that do not possess LPS, as various PAMPs can cause immune overstimulation while other virulence factors protect bacteria from host killing or facilitate easier access to the bloodstream (eg, GBS beta-hemolysin destroys alveolar linings, allowing bacteria to enter the blood).[68] The immune response in neonates also demonstrates subtle differences in character that may predispose it to dysregulation such as lower L-selectin adhesion molecule expression and impaired formation of neutrophil extracellular traps (NETs) that hinder neutrophil killing of pathogens at the local stage.[45,69,70]

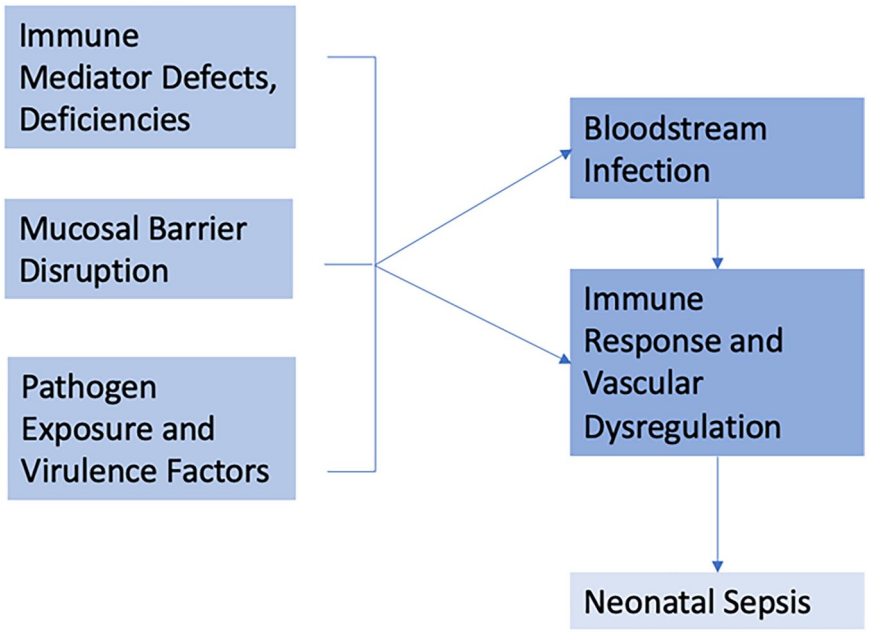

Figure 1. Key risk factors and events in the pathophysiology of neonatal sepsis.

Changes in vascular permeability are a central driver of both the symptomatic presentation of sepsis and the end-organ damage it can cause. Overproduction of vasodilators like prostaglandins, leukotrienes and nitric oxide (via overexpression of inducible nitric oxide synthases) following pro-inflammatory stimulation increases fluid extraversion from the systemic circulation, leading to hypotension and eventually organ hypoperfusion and damage.[71,72]

Current research suggests that the magnitude of anti-inflammatory compensation, which often occurs in conjunction with rather than following a proinflammatory response, is also a significant indicator of outcome.[45,73] Early production of interleukin-10 (IL-10), an anti-inflammatory cytokine which reduces neutrophil recruitment to sites of local inflammation, was found to be associated with lower survival rates in neonatal mice with GBS-induced sepsis, and when IL-10 effects were blocked, outcomes improved.[74] The interplay and role of pro-inflammatory and anti-inflammatory mediators in both the attenuation and stimulation of SIRS in the presence of infection are thus very complex and time sensitive.

A summary of the key contributors to the pathophysiology of neonatal sepsis is shown in Figure 1.

Presentation, Diagnosis and Biomarkers

While the SIRS criteria and Quick Sequential Organ Failure Assessment (qSOFA) score are clinically established methods to diagnose sepsis in adults, they rely on indicators of homeostatic instability that occur later in the disease course of neonatal sepsis (when the mortality rate has already reached unacceptable levels).[75] Additionally, babies with sepsis can present asymptomatically or with non-specific symptoms.[76,77]

This being said, poor feeding, subcostal and intercostal contractions, bradycardia, tachycardia, vomiting, cyanosis, high-pitched crying, fever, hypotonicity, jaundice, petechiae, convulsion, lethargy, diminished sucking reflex and groaning are all commonly reported clinical findings.[78-80] The presence of any of these features should prompt investigation for sepsis if there are no strong alternative explanations for them.

Blood culture is the first-line investigation with the greatest evidence-backing and should be done rapidly following initial suspicion of neonatal infection. The time to positivity (ie, time taken for pathogenic organisms to grow from the time of inoculation) of suspected EOS blood cultures is between 97% and 100% in 48 hours, suggesting that antibiotic use may be safely reduced after 2 days of admission if clinical assessment does not suggest further investigation.[81,82]

According to British National Institute for Health and Care Excellence (NICE) guidelines, If blood culture is positive, a lumbar puncture should be performed.[83] Signs of CNS dysfunction, lack of response to antibiotic treatment and the presence of clinical features or laboratory results strongly suggestive of neonatal sepsis should also be followed up with a lumbar puncture, even if blood cultures are negative.[56,84] This is as slow-growing or culture-negative causative pathogens, inadequacies of specimens taken and antibiotic use can all produce false negatives despite improvements in blood culture detection technology.[85] Consequently, Polymerase chain reaction (PCR) can be performed on culture-negative blood samples, with 1 study showing PCR identifying organisms in 45% of culture-negative cases of suspected EOS.[86,87] PCR and culture can also be performed on the cerebrospinal fluid (CSF) obtained from lumbar puncture.[88] Reductions in CSF glucose concentration and elevations in protein and white blood cell

(WBC) levels may point to an ongoing bacterial infectious process.[2,89]

While it is important not to prematurely rule out sepsis, the absence of an elevation in the proportion of immature neutrophils (immature neutrophils:total neutrophils <0.27) has been shown to have a high negative predictive value (NPV) for neonatal sepsis. However, elevations in this proportion are often physiological in many cases, limiting the usefulness of this measure as a diagnostic tool.[90,91] Still, this ratio shows higher sensitivity than absolute neutrophil or neutrophil band levels.[68] Leukocyte count and platelet count have also been shown to be significantly lower in neonatal sepsis cases compared to controls and may also be employed in the diagnostic workup.[92]

Raised C-reactive protein (CRP) levels are characteristic of bacterial infection, as CRP is an acute phase protein produced by the liver that functions to promote opsonisation and phagocytosis of bacteria by binding to their polysaccharide capsules and facilitating complement blinding.[93,94] However, CRP, along with other acute phase proteins and white blood cells, can be raised in many acute inflammatory states as well as during normal foetal and neonatal development.[95,96] Similar to the immature:total neutrophil ratio, a lack of a rise in CRP is a feature that provides exclusionary utility, particularly if CRP levels remain normal 36 hours after the first administration of empirical antibiotics, as this period has been shown to be where CRP's NPV plateaus.[97] Since CRP requires various upstream transcriptional signals to be produced, levels do not significantly rise until about 10 to 12 hours after infection, making it a relatively late marker of the infectious process.[98,99]

IL-6, an inflammatory cytokine produced by lymphocytes, is an important stimulator of CRP transcription.[100] As such, its levels rise before CRP levels do in response to infection, and it can thus potentially suggest neonatal sepsis earlier in the disease course.[98] Unfortunately, IL-6 has a very short half-life, which limits the timeframe in which it can be used as a reliable biomarker.[98,100]

Procalcitonin (PCT) is a calcitonin hormone precursor, which is produced physiologically at low concentrations by the thyroid gland in the process of calcium regulation but also by monocytes at an early stage in response to bacterial LPS.[101] It has been shown to be a more sensitive acute phase reactant than CRP for the diagnosis of neonatal sepsis, with a 2019 meta-analysis finding PCT to have an 8% higher mean sensitivity for EOS and a 11.5% higher mean sensitivity for LOS compared to CRP.[102] This being said, mean sensitivity of PCT was still only found to be 73.6% for EOS, and this entails that many neonatal infections will still go undetected, particularly at a more actionable stage.[102,103] Unfortunately, this issue reflects a wider problem with neonatal sepsis biomarkers currently in use in that their relatively suboptimal sensitivity remains a salient factor in the high morbidity and mortality of the condition.[24] More investigation on how to successfully implement early-phase and high sensitivity biomarkers as well as other diagnostic techniques with similar attributes into clinical practice is thus pertinent in advancing the overall outlook of neonatal sepsis management.[104]

Prevention, Treatment and Management

Prevention strategies are a crucial factor behind EOS incidence reduction. Maternal intrapartum intravenous antibiotic administration with penicillin (or clindamycin for those with serious penicillin allergy) should ideally be given for at least 4 hours before delivery to target GBS in mothers with established GBS infection or those with relevant EOS risk factors.[56,105] These risk factors include having a previous infant with invasive GBS disease, current GBS bacteriuria, rupture of membranes >18 hours and fever in the mother.[56,105] Efforts to reduce prematurity rates, such as by improving maternal nutritional status and broader prenatal care, may also reduce neonatal sepsis incidence.[106,107]

In those with suspected EOS, broad-spectrum antimicrobials should be used until the causative pathogen can be isolated and more guided therapy can be employed. A combination of intravenous aminoglycoside and either ampicillin (US guidelines) or benzylpenicillin (UK guidelines) is currently used in most settings, as this regime provides extended cover for both potential gram-positive and gram-negative sources (https://www.nice.org.uk/guidance/ng195).[53,108,109,110] In low and middle-income countries, treatment often poses additional challenges, as there can be very high rates of resistance to this standard antibiotic therapy (particularly among gram-negative isolates) as well as technological and diagnostic limitations that hinder transitions to guided therapy.[111]

Prevention of LOS can be best achieved by mitigating potential pathogen entry routes through reducing unnecessary intervention in neonatal intensive care units (eg, avoiding premature changing of central lines) and improving hygiene practices such as ensuring adequate hand washing.[28,112,113]

LOS infections should normally be treated in line with guidance and incidence-data from local hospital boards. In addition to the antibiotic regime used for EOS, cephalosporins and vancomycin are also often employed due to their higher efficacy against the beta-lactamase-producing *Staphylococcus* bacteria more frequently encountered in LOS.[53,114]

It's important to note that there is variance between guidelines in different countries regarding when to investigate for neonatal sepsis or prescribe antibiotics. Table 3 compares the relevant criteria in the UK NICE guidelines and American Academy of Paediatrics (AAP) recommendations for EOS.[66,108,115] The inclusion of the Kaiser Permanente Sepsis Risk Calculator (SRC) as a tool in diagnosis and management is somewhat controversial, although its use is mentioned as a viable strategy in both sets of guidelines. This calculator takes into account regional EOS incidence, type of prophylaxis used, maternal GBS status and intrapartum temperature (highest value), time between membrane rupture and birth and gestational age to calculate whether there

Table 3. Key considerations from nice guidelines and aap guidelines for management of early-onset neonatal sepsis.[53,108,115]

NICE GUIDELINES	AAP GUIDELINES
Presence of 'red flag' risk factor (ie, previous pregnancy with suspected/confirmed infection in baby) or a 'red flag' clinical Indicator (apnoea, seizures, mechanical ventilation requirement, signs of shock etc.) requires immediate antibiotics + investigation	Multivariable Analysis with the Kaiser-Permanente Sepsis Risk Calculator that yields a EOS risk estimated at ⩾3 per 1000 live births should be followed up with empirical antibiotics and relevant investigations while those with a risk of ⩾1 per 1000 live births should receive enhanced clinical observation and a blood culture; This is 1 of 3 outlined approaches that are equally recommended
Presence of 2 or more 'non-red flag' risk factors (invasive GBS infection in previous child of multiparous woman, rupture of membranes >18 h, chorioamnionitis diagnosis, preterm birth <37 mo gestation etc.) or 2 or more 'non-red flag' clinical indicators (feed intolerance, abnormalities in muscle tone, glucose level, heart rate, respiratory effort or acid-base status etc.) also requires immediate antibiotics + investigation	2nd approach (risk-factor based): suggests lab investigation and empirical antibiotics for any ill-appearing newborn or baby born to a mother with chorioamnionitis; For neonates born to a GBS-infected mother with inadequate prophylaxis, only laboratory investigation is recommended if rupture of membranes >18 h or preterm birth <37 mo gestation while observation for ⩾48 h is the sole recommendation if either of these 2 additional factors are not present
If only 1 'non-red flag' risk factor or 'non-red flag' clinical indicator is present without any 'red flag' risk factors or clinical indicators, decision to prescribe antibiotics and perform investigations should be based on clinical judgement and can be adjusted based on continued monitoring	3rd approach: based on serial clinical observations and relies on the presence of clinical indicators to guide the prescribing of antibiotics or initiation of investigations
Kaiser Permanente Neonatal Sepsis Calculator is mentioned as an alternative approach to these guidelines	

will be a clinical benefit with antibiotic prescription (depending on the baby's clinical presentation). The score is, however, limited to evaluating babies with gestational age >34 weeks.[113,116,117]

Resistant organisms are a significant burden in both high and low-income countries, with multidrug-resistant (MDR) organisms estimated to be responsible for 30% of deaths linked to neonatal sepsis globally in 2016.[118] In 1 Singapore healthcare setting, MDR isolates were found in 47% of neonatal sepsis infections.[119] The incidence of Gram negative MDR isolates in particular has been increasing, and high levels of resistance to first and second-line antibiotics currently being used in neonatal sepsis guidelines is being seen on a global scale.[118,120-122] As these revelations drive the usage of novel and less-commonly used and older antibiotics (eg, Fosfomycin) in neonatal populations, the data on safety profiles and appropriate dosing for these drugs may become worryingly scarce and in need of further investigation.[118,121]

In addition to antibiotic resistance, antibiotic use in neonates is itself linked to necrotising enterocolitis development, autoimmunity later in life and other long-term effects.[123-125] The gut microbiome plays a key role in the synthesis and availability of many inflammatory mediators and their precursors, and antibiotic use can disturb the composition of the microbiome at a critical stage in infancy, potentially giving rise to aberrant immune responses and promoting the growth of pathogenic bacteria.[126] Disruptions in gut flora may also cause changes within the gut-lung, gut-skin and gut-brain axis that have been implicated in the pathogenesis of various diseases.[127,128] As a result, although there have been limited trials to determine the reliability and accuracy of current neonatal sepsis scoring systems, the Kaiser Permanente SRC is seeing increased usage in hospitals seeking to reduce unnecessary antibiotic usage.[108] Serial observations may also help guide appropriate reductions in antibiotic administration.[129]

Adequate management of the thermoregulatory and hemodynamic dysfunction that develops as part of a SIRS is a key factor in reducing mortality.[130] Intravenous fluids and nutrition are regularly indicated along with the transfusion of blood products. Incubator/radiant warmers can be employed to control neonatal temperature and humidity.[2,130]

Intravenous immunoglobulin (IVIG) is sometimes considered in management strategies due to the theoretical enhancement it gives to the neonatal humoral immune response in addition to aiding in volume repletion. However, the transient nature of effects recorded, adverse effects and cost and sourcing considerations combined with most current data showing no clear reduction in mortality potentially suggest against its usage in this case.[131,132]

Additional Recent Developments

Much of the current/recent research into sepsis affecting neonates has been focused on the discovery of novel biomarkers that will aid in the diagnosis of the condition, as late or missed diagnosis is a major factor in the high mortality of neonatal sepsis.[133] At the same time, the lack of definitive diagnostic methods reduces discrimination in antibiotic use and is likely linked to the growing number of antibiotic-resistant sepsis deaths (especially seen in developing countries).[134] Activin A, a member of the transforming growth factor-β (TGF-β) cytokine family, and serum amyloid A, an acute phase protein, are 2 molecular components of sepsis pathways that have shown higher sensitivity compared to more widely used markers like CRP, with their levels also rising at an earlier point in the disease course.[6,135] The value of such markers is further

underscored by the low levels of bacteraemia needed to cause disease in infants (which can hinder culturing ability) and increasing focus/awareness regarding non-bacterial pathogens causing sepsis symptoms.[16,136]

Metabolomics is an emerging field looking at the presence and concentration of certain metabolites/molecules produced in biological processes implicated in neonatal sepsis.[137] Technology employed in metabolomics, which has already been used to study infectious disease in adults and children, offers potential to both understand pathophysiological unknowns related to the development of neonatal sepsis and its differentiation from sepsis in other age demographics as well as to detect certain molecular patterns that are unique to the disease process and which, therefore, can be used to identify cases with more reliability.[138,139] The potential advantage of metabolomics in diagnostics over traditional biomarkers and PCR lies in its ability to discern complex and time-dependent changes in phenotypic expression that underlie the variability and nuances particularly present in the molecular development of neonatal infections.[138,140] Through metabolomic analysis, catabolites of glutathione and tryptophan pathways have been found to be raised in septic neonates. These pathways are thought to be involved in anti-inflammatory deficiencies/differences that increase sepsis susceptibility among infants. More research is ongoing to characterise these changes and additional metabolic alterations in view of improving conceptual understanding of neonatal sepsis and discovering valuable, new biomarkers.[138-140]

Given the limited options currently available to treat neonatal sepsis, there is great interest in the potential role of immunomodulation (eg, with granulocyte colony-stimulating factor or the aforementioned IVIG) in reducing sepsis rates and mortality.[141] Success rates reported in recent trials is mixed, and more data needs to be collected clinically to realise and evaluate the translatability of strategies derived from knowledge of biochemical pathways and animal studies.[141,142] Administration of Pentoxifylline, a phosphodiesterase inhibitor, was found in 1 meta-analysis (comprising of 6 randomised control trials) to reduce all-cause mortality when used as an adjunct to antibiotics, while another meta-analysis looking at the effect of supplementation with the antimicrobial protein lactoferrin showed a reduction in incidence of the bacterial and fungal sepsis in neonates but no effect on mortality or hospital stay duration.[142-144] Trained immunity, where an immune challenge is given in a non-lethal dose to improve innate immune mechanisms and protect against future sepsis, is also a key area of study, with 1 study showing improved survival in an experimental group of mice that were intraperitoneally given a non-lethal/low-dose septic challenge a few days before being receiving a lethal septic challenge dose.[141,145,146]

In regards to COVID-19 and its ability to cause sepsis/sepsis-like presentations in neonates, as the expression of TMPRSS2 and ACE2 (transmembrane proteins that facilitate Sars-Cov-2 cellular entry) has been shown to be limited in the placenta, there is still ambiguity about the ability of the virus to be transmitted transplacentally and the mechanism for such transmission.[147] Furthermore, neonatal infection with COVID-19 is uncommon and largely asymptomatic, and a recent UK Obstetric Surveillance System study found only 5% of babies born to COVID positive mothers to be COVID positive themselves.[148,149] To date, there have been very few recorded cases of neonatal sepsis due to COVID-19, with 1 male premature infant with COVID-19 EOS showing a positive outcome after being treated with IVIG and corticosteroids in addition to receiving intubation and intratracheal surfactant.[150] The relatively lower incidence and milder presentation of neonatal COVID-19 infection compared to adult COVID-19 may be due to differences in ACE2 receptor distribution and density and less adaptive immune system-driven cytokine overactivity in neonates, but the specific pathophysiology and long-term sequelae of COVID-19 in infants are still largely unknown.[148,151,152]

Complications

Complications of neonatal sepsis result from both hemodynamic stress/insufficiency as well as potential damage incurred from inflammatory mediators.

Sepsis may progress to septic shock, where persistent hypotension occurs along with largely hypoperfusion-driven end-organ damage in multiple sites. This results in acute multi-organ failure and increases the probability of death substantially.[153-155] Other factors associated with higher mortality are low birthweight and the presence of sclerema neonatorum (hardening of subcutaneous tissue).[156,157,158]

EOS is also associated with higher rates of respiratory distress and overall mortality than LOS, with global mortality estimates being 16.4% for EOS and 9.1% for LOS.[4,158]

Bacterial antigens, together with inflammatory factors, stimulate tissue factor synthesis and downregulate anti-coagulative pathways, leading to a prothrombotic state and, in severe cases, disseminated intravascular coagulation (DIC).[159,160]

Neonatal bacterial meningitis is another common complication of neonatal sepsis that occurs when septicaemia spreads to the meningeal linings. IL-6 and TNF-α are among the cytokines upregulated in sepsis that are brought into the brain via endothelial receptor-mediated endocytosis, where they can then activate microglial cells. Microglia stimulate apoptosis of neurons and neuronal damage through increased generation of reactive oxidative species and other inflammatory mechanisms. This may result in permanent brain damage that is reflected in the higher rates of neurological disorders like cerebral palsy seen in survivors of septic meningitis.[161,162]

Conclusions

The incredible complexity of foetal and neonatal development would not be possible without nourishment from the mother and the outside world. However, these sources of life and growth

also provide a portal of entry for microorganisms that can take advantage of differences between not only neonatal and adult immunity, but also between neonates at different developmental stages. Increased research needs to be undertaken to better understand these differences in order to further develop our knowledge of unique neonatal risk factors and what can be done to mitigate these.

Additionally, while progress has been made regarding mortality rates, the incidence of neonatal sepsis, especially in preterm infants and in low-income countries, remains worryingly high. It is vital that thorough screening for maternal infection and other risk factors is more widely implemented, with preventive prophylaxis employed in all relevant circumstances. Progression of infection to the inflammatory challenges that sepsis entails can be especially rapid in the neonatal demographic and is more often accompanied by dramatic hemodynamic changes that may emerge unexpectedly from an asymptomatic picture. As such, improving detection and understanding of markers with high specificity and sensitivity should be another priority among neonatologists.

Lastly, although current antibiotic guidelines are effective in treating many of those affected, growing antibiotic resistance, late diagnosis and cases that have a non-bacterial aetiology or are otherwise nonresponsive necessitate more investigation into alternative treatment strategies and their effectiveness. The impact of intervention, including antibiotic use, on future development and infection risk should also be considered.

Declarations

Ethical approval

The authors are accountable for all aspects of the work, including ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Consent for publication and consent to participate

Not applicable, as there are no published figures, tables or videos that have been reproduced and this article does not contain any studies with human or animal subjects performed by any of the authors.

Author contributions

Adi Raturi and Suresh Chandran contributed to the article's conception and design. Research and resource collection was done by Adi Raturi and Suresh Chandran. The first draft of the manuscript was written by Adi Raturi. All authors reviewed the final manuscript.

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None.

Availability of data and materials

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Strengths and limitations

This review article includes studies from low and middle-income countries as well as developed countries. We aimed to provide a broad synthesis of the current and novel knowledge around this topic, but each area explored can be elaborated on further in more specific reviews and, conversely, all the latest developments could not be included in this singular article.

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