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REVIEW ARTICLE

Challenges in developing a consensus definition of neonatal sepsis

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Sepsis remains a leading cause of morbidity and mortality in the neonatal population, and at present, there is no unified definition of neonatal sepsis. Existing consensus sepsis definitions within paediatrics are not suited for use in the NICU and do not address sepsis in the premature population. Many neonatal research and surveillance networks have criteria for the definition of sepsis within their publications though these vary greatly and there is typically a heavy emphasis on microbiological culture. The concept of organ dysfunction as a diagnostic criterion for sepsis is rarely considered in neonatal literature, and it remains unclear how to most accurately screen neonates for organ dysfunction. Accurately defining and screening for sepsis is important for clinical management, health service design and future research. The progress made by the Sepsis-3 group provides a roadmap of how definitions and screening criteria may be developed. Similar initiatives in neonatology are likely to be more challenging and would need to account for the unique presentation of sepsis in term and premature neonates. The outputs of similar consensus work within neonatology should be twofold: a validated definition of neonatal sepsis and screening criteria to identify at-risk patients earlier in their clinical course.

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IMPACT:

- There is currently no consensus definition of neonatal sepsis and the definitions that are currently in use are varied.
- A consensus definition of neonatal sepsis would benefit clinicians, patients and researchers.
- Recent progress in adults with publication of Sepsis-3 provides guidance on how a consensus definition and screening criteria for sepsis could be produced in neonatology.
- We discuss common themes and potential shortcomings in sepsis definitions within neonatology.
- We highlight the need for a consensus definition of neonatal sepsis and the challenges that this task poses.

INTRODUCTION

Infection remains one of the leading causes of neonatal morbidity and mortality worldwide.[1–5] It is estimated that approximately 22/1000 live births develop neonatal sepsis with a case mortality of between 11% and 19% for those affected.[1] While there is a very strong association between socioeconomic status and sepsis mortality,[6] neonatal sepsis is an important health issue internationally. Neonates have altered innate and adaptive immune responses to infection compared to adults.[7] Lower innate cell numbers and activity, reduced pattern recognition receptor responses, altered cytokine activity and reduced adaptive immune response compared to the adult population mean that neonates are at especially high risk of bacterial sepsis.[7] Neonates are also exposed to unique environmental factors that may predispose them to infection such as maternal colonisation with group B streptococcus, prolonged rupture of membranes and chorioamnionitis.

Neonatal sepsis accounts for 15.6% of neonatal mortality worldwide.[8] Neonates are at increased risk of infection compared to older children and the presentation within the neonatal

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population is often non-specific with common presentations, including alterations in feeding, lethargy and respiratory distress.[5] Clinicians must therefore have a low threshold for investigating and treating neonates with suspected sepsis due to the increased risk and often subtle presentation. Suspected infection and sepsis are therefore among the commonest causes of neonatal hospital admission[9,10] and represent areas of considerable healthcare expenditure.[11] In addition, sepsis can lead to a variety of short- and long-term complications within the neonatal population.[12,13] The risk is particularly high in premature neonates who have a more pronounced immaturity in innate and adaptive host defence mechanisms and require increased medical intervention that may disrupt normal anatomical barriers.[14] There is also a strong inverse relationship between the incidence of sepsis and both gestational age and birth weight.[15] Premature neonates with sepsis are at high risk of multi-organ dysfunction.[16] Their mortality rate during sepsis may be as high as 35% in cases of early-onset sepsis (EOS)[17] and between 18% and 36% in late-onset sepsis (LOS).[18] EOS is generally considered to be acquired vertically or in the peripartum period, whereas LOS is frequently a healthcare-associated infection, most commonly seen in medically complex, premature neonates. While the aetiology of EOS and LOS differ, both have been linked to adverse short- and long-term outcomes. Meta-analysis suggests that both surviving term and premature neonates are at high risk of later neurodevelopmental impairment and cerebral palsy,[19,20] though true estimation of long-term sepsis-related morbidity is hampered by investigators using differing criteria for the diagnosis of sepsis.

While definitions vary greatly between sources, there is a traditional view that infection, sepsis and septic shock represent distinct but related entities. Infection is generally used as an umbrella term for any suspected or proven infective process, regardless of aetiology or severity.[21] Within paediatrics, sepsis has classically been defined as a syndrome of systemic inflammation with resultant clinical or laboratory abnormalities in the presence of proven infection,[21] most commonly a positive blood culture. The Sepsis-3 group has recently defined sepsis in adults as "life-threatening organ dysfunction caused by a dysregulated host response to infection".[22] Sepsis-3 has recently defined septic shock in adults as a subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality.[22]

Owing to the high mortality in the neonatal period,[23] maternal and neonatal infection have been identified as high-priority areas for clinicians and researchers worldwide.[24] In recent years, the incidence of neonatal infection and the resulting mortality have lessened considerably due to advances in medical care,[25] and the availability of a consensus definition of neonatal sepsis would be a logical step in continuing the progress in this area. At present, no unified international definition of neonatal sepsis exists, and the currently employed definitions vary considerably.[26] Attempts have previously been made to produce consensus definitions for paediatric sepsis, such as those of the European Medicines Agency[27] and the International Consensus Conference on Pediatric Sepsis.[28] However, these definitions are not specifically designed for neonatal intensive care unit (NICU) patients and do not address sepsis in premature neonates. There is increasing recognition that a validated consensus definition of neonatal sepsis is a critical step to improve identification and treatment of septic neonates and improve related outcomes.[29] In addition, a unified definition of neonatal sepsis could potentially limit the use of antibiotics, assist in identifying those neonates at risk of neurodevelopmental complications and facilitate comparison of sepsis-related research outcomes. Such a definition would have to clearly identify sepsis early in its clinical course and would need to address the unique problems of diagnosing sepsis and screening for organ dysfunction in premature neonates.

Here we aim to discuss the existing definitions of neonatal sepsis employed by neonatal research and surveillance networks internationally with reference to the recent progress made in the Sepsis-3 consensus statement from adult populations.

METHODS

A Pubmed search was undertaken to identify experimental and observational studies from neonatal surveillance and research networks with specified criteria for the diagnosis of neonatal sepsis. The following search string was used: ((neonat*[Title] OR preterm[Title] OR premature[Title])) AND (sepsis[Title] OR infection [Title]). Publications were limited to those in English, performed in human neonates (<1 month) and published by international neonatal surveillance and research networks. Observational studies, interventional studies and review articles were included, and the references of relevant studies were also reviewed. Owing to manuscript length, randomised controlled trials (RCTs) were not included and will be discussed in a separate manuscript. The networks identified to have published relevant definitions in their work were: the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Neonatal Research Network, The Australian and New Zealand Neonatal Network (ANZNN), the Vermont Oxford Network (VON), the Neonatal Infection surveillance Network (NeonIN), Canadian Neonatal Network; Australasian Study Group for Neonatal Infections (ASGNI), The Centre for Disease Control and Prevention (CDC), and NeoKISS (Supplementary Fig. S1). If a data dictionary, surveillance report or definitions manual of a network was published online, this was also accessed (Table 1).

Despite the many differences that exist between definitions used, there are common themes that are frequently encountered. Neonatal sepsis definitions will be discussed in the following areas: infective organism/microbiology, duration of therapy, contaminants and polymicrobial cultures, coagulase-negative staphylococcal (CONS) sepsis, timing of sepsis, clinical signs and culture-negative sepsis, laboratory data, and subclassification of sepsis.

Adult sepsis definitions and their utility in childhood

Improving definitions of sepsis and septic shock within the adult population have been a focus of the Sepsis-3 publications, and the resulting definitions have been successfully incorporated into the Surviving Sepsis campaign.[22,30] The Sepsis-3 consensus work by Singer et al.[22] addressed many of the existing challenges in defining sepsis such as the use of heterogenous definitions, the lack of consensus on terminology, the need to relate diagnosis to outcome and the need for screening tools to identify patients with sepsis and septic shock. This expert group performed systematic literature reviews,[31,32] face-to-face meetings and subsequently convened a Delphi to decide on clinical criteria and definitions used. The suggested definitions of sepsis and the criteria for sepsis screening were validated in large health databases within the US and peer-reviewed by major international societies in the field. The result is a comprehensive, evidence-based approach to the definition and diagnosis of sepsis and septic shock in the adult population with a robust screening tool, the sequential organ failure assessment (SOFA) score and the quick SOFA (qSOFA), to allow earlier screening and treatment of at-risk patients (Table 2). The definitions used eschewed previously used terms such as "SIRS" and "severe sepsis" in favour of a simple, validated, clinically focussed approach to the definition of sepsis and septic shock with more emphasis on organ dysfunction and less on traditional microbiological results.

The presence of organ dysfunction in adults with suspected sepsis has been shown to increase mortality substantially in the intensive care setting.[33] In addition, a linear relationship between the number of organs impaired and sepsis-related mortality[34] reflects the importance of organ dysfunction in predicting outcome. Sepsis-3 have therefore defined sepsis as

Table 1. Summary of the criteria of each organisation discussed.

Organisation	Early-onset sepsis	Late-onset sepsis	Pathogens	Culture/PCR	Duration of therapy	Contaminants	Polymicrobial culture	Interval between episodes	CONS Sepsis	Clinical signs	Culture negative	Laboratory data	Subclassification
National Institute of Child Health and Human Development (NICHD)[17,51–63]	Positive culture ≤72 h of life	Positive culture >72 h of life	Bacteria and fungi	CSF culture Blood culture	≥5 days of antibiotic therapy required	Specific list of contaminants provided	Approach varied between studies	>10 days between isolates of the same organism or a new organism cultured at any time	Additional clinical or laboratory criteria required with positive culture	Required in some studies, not defined	Recognised in one publication, specific criteria provided	Required in CONS sepsis only	Meningitis classified separately CONS: "definite", "possible", "contaminant"
Australian and New Zealand Neonatal Network (ANZNN)[65,89]	<48 h at the time of symptom onset	≥48 h at the time of symptom onset	Bacterial, fungal and viral[b]	CSF culture Blood culture PCR on CSF	Not specified	Only CONS specifically discussed	Not discussed	>14 days between isolates of the same organism	Not discussed	Required but not defined	Not recognised	Not required	Not discussed
Vermont Oxford Network (VON)[66]	≤3rd day of life	>3rd day of life	Bacteria or fungal	CSF culture Blood culture	≥5 days of antibiotic therapy specified for CONS sepsis only	Only CONS specifically discussed	Polymicrobial culture may be diagnosed	Not specified	Signs of generalised infection, ≥5 days antibiotic therapy and positive culture	Required for CONS only, examples provided	Not recognised	Not required	Meningitis included with sepsis
Neonatal infection network (NeonIN)[67,68]	≤48 h at the time of positive culture	>48 h at the time of positive culture	Bacteria	CSF culture Blood culture Suprapubic aspirate	≥5 days of antibiotic therapy required	Specific contaminants not specified	Not discussed	≥7 days between repeat bacterial isolates ≥10 days between repeat CONS isolates ≥14 days between repeat fungal isolates	≥5 days of antibiotic therapy with positive culture	Not discussed	Not recognised	Not required	Not discussed
Canadian Neonatal Network[69,70]	≤48 h at the time of positive culture	>48 h at the time of positive culture	Bacteria, fungal and viral	CSF culture Blood culture	≥5 days of antibiotic therapy for clinical sepsis and in potential contaminants	List of common skin contaminants provided	Polymicrobial culture may be diagnosed	≥7 days between isolates of the same organism or a new organism cultured at any time	Positive culture in the setting of LOS	Required, specific list provided	Recognised, specific criteria provided	One of the several possible criteria that may be used	CVC-related sepsis classified separately, meningitis/ ventriculitis listed
Australasian Study Group for Neonatal Infections (ASGNI)[71,72,80–82]	≤48 h at the time of onset[a]	>48 h at the time of onset[a]	Bacteria or fungal	CSF culture Blood culture	Not specified	Specific contaminants not specified	Approach varied between studies	Not specified	Positive culture in the setting of LOS	Required, examples provided	Not recognised	Occasionally[c]	Bacterial and fungal meningitis defined separately
Neo-KISS[73]	Excluded	>72 h after birth or admission at the time of symptom onset is "nosocomial"	Bacteria, fungal or viral	CSF culture Blood culture	≥5 days of antibiotic therapy specified for clinical sepsis only	Only CONS specifically discussed	Not discussed	An infection-free period of 14 days is required	Additional laboratory criteria with positive culture	Required, specific list provided	Recognised, specific criteria provided	One of the several possible criteria that may be used	CVC-related sepsis classified separately, meningitis not discussed
Centre for disease control and prevention (CDC)[64,79]	<7 day at the time of positive culture	≥7 days at time of positive culture	Bacteria	Culture from a normally sterile site	Not specified	Specific list of contaminants provided	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed	Not required	Not discussed

CSF cerebrospinal fluid, *CONS* coagulase-negative staphylococcus.
[a]Unclear whether symptoms or cultures.
[b]Separate diagnostic criteria were required for viral sepsis in ANZNN publications.
[c]Required in some publications to differentiate contaminants from true sepsis.

Table 2. Comparison of organs dysfunction measurement tools in from Sepsis-3 (SOFA and qSOFA) and a suggested adaptation for the neonatal population (nSOFA).

SOFA (sepsis-related organ failure assessment) score criteria

	Score				
System	1	2	3	4	5
Respiratory PaO_2/FIO_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2–1.9 (20–32)	2.0–5.9 (33–101)	6.0–11.9 (102–204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 μg/kg/min or dobutamine (any dose)	Dopamine 5.1–15 μg/kg/min or epinephrine ≤0.1 μg/kg/min or norepinephrine ≤0.1 μg/kg/min	Dopamine >15 μg/kg/min or epinephrine >0.1 μg/kg/min or norepinephrine >0.1 μg/kg/min
Central Nervous System Glasgow Coma Scale score	15	13–14	10–12	6–9	<6
Renal Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2–1.9 (110–170)	2.0–3.4 (171–299)	3.5–4.9 (300–440)	>5.0 (440)
Urine output, mL/day				<500	<200

qSOFA (Quick SOFA) score criteria

Respiratory rate ≥22/min

Altered mentation

Systolic blood pressure ≤100 mm Hg

Proposed nSOFA (neonatal SOFA) score

	Score				
Respiratory	0	2	4	6	8
	Not intubated OR intubated, SpO_2/FiO_2 ≥300	Intubated, SpO_2/FiO_2 <300	Intubated, SpO_2/FiO_2 <200	Intubated, SpO_2/FiO_2 <150	Intubated, SpO_2/FiO_2 <100
Cardiovascular	0	1	2	3	4
	No inotropes AND no systemic steroids	No inotropes AND systemic steroid treatment	One inotrope AND no systemic steroids	Two or more inotropes OR one inotrope AND systemic steroid treatment	Two or more inotropes AND systemic steroid treatment
Platelets ($10^3/\mu L$)	0	1	2	3	
	Platelet count $\geq 150 \times 10^3$	Platelet count 100–149 $\times 10^3$	Platelet count $<100 \times 10^3$	Platelet count $<50 \times 10^3$	

"life-threatening organ dysfunction caused by a dysregulated host response to infection" and septic shock as a "subset of sepsis in which underlying circulatory and cellular/metabolic abnormalities are profound enough to substantially increase mortality".[22] The Sepsis-3 group state that organ dysfunction may be occult and that it should be considered in any patient presenting with infection; in addition, any unexplained episodes of organ dysfunction should prompt screening for sepsis.[22] The increased focus on organ dysfunction in updated definitions reflects the fact that organ dysfunction is not only a key criterion for the early diagnosis of sepsis but the degree of organ dysfunction is also of prognostic importance in patients both during and after episodes of sepsis.

To screen high-risk patients, the group devised the qSOFA, which is an abridged version of the longer SOFA score used to identify organ dysfunction in sepsis.[32] The qSOFA can be performed at the bedside and requires only 2 of the following criteria as a positive screening test for sepsis: increased respiratory rate >22/min, systolic blood pressure (BP) <100 and altered mentation. Having a positive qSOFA identifies the patients with suspected sepsis who are likely to have a prolonged ICU stay and increased mortality. In the setting of infection, qSOFA ≥2 acts as a good screening test for sepsis and should prompt clinicians to investigate more thoroughly for organ dysfunction using the longer SOFA score and consider initiation of therapy. The criteria for the diagnosis of septic shock requires both of the following to be present in the setting of sepsis where fluid resuscitation has been adequately undertaken: necessity for vasopressors to maintain mean arterial pressure ≥65 mm Hg and serum lactate >2 mmol/L.[31] Criticisms levelled against the new diagnostic and screening approach include issues around qSOFA sensitivity, the lack of applicability in resource-poor settings and a fundamental disagreement with the idea that sepsis requires organ dysfunction.[35] Systematic reviews evaluating Sepsis-3 screening criteria have noted that a positive qSOFA is a more sensitive predictor of mortality in emergency department patients with sepsis[36]; is strongly associated with mortality in pneumonia[37] and has improved specificity for ICU admission, organ dysfunction and mortality[38] when compared to a traditional screening criteria. However, these reviews have all noted that there are concerns about the sensitivity of qSOFA in isolation, and owing to the limited pool of research to date, there is considerable heterogenicity between the studies included in each review. The Sepsis-3 group has acknowledged that, while limitations do exist in the definitions and tools developed, no approach will be all encompassing,[22] and the qSOFA and SOFA represent simple, outcome-based screening tools that have been validated within existing healthcare databases.

Attempts have been made to apply principles from the Sepsis-3 group in the paediatric setting with adaptation of the SOFA score to create a paediatric SOFA (pSOFA) by adjusting physiological parameters to age-related cut-offs.[39] pSOFA was then used to test the Sepsis-3 definitions in patients aged <21 years admitted to ICU with confirmed or suspected sepsis and confirmed the utility of Sepsis-3 parameters in the paediatric population.[39] Subsequent work in a mixed paediatric intensive care cohort using similarly adjusted SOFA and qSOFA scores showed improved diagnostic performance compared to other organ scoring systems,[40] again highlighting the potential utility in younger patients. Most recently, the Sepsis-3 definitions have been used within a mixed paediatric cohort in an emergency department setting and showed that qSOFA has moderate prognostic accuracy in predicting mortality and/or paediatric ICU admission.[41] Despite this initially promising work, there remains some debate as to the utility of Sepsis-3 work within paediatrics.[42–44] Similar work is lacking in neonatology, though Wynn et al. have reviewed the literature on paediatric sepsis and found that definitions currently in use among paediatric populations are not accurate in term and premature neonates.[26] Wynn and Polin have suggested that the existing Sepsis-3 work could be adapted to a neonatal setting and have proposed a neonatal-specific SOFA (nSOFA),[29] and early work has suggested that this may predict mortality in very low birth weight (VLBW) neonates with LOS[45] (Table 2). The National Institute for Health and Care Excellence (NICE) guidelines have adopted the adult definitions of Sepsis-3 but do not specify terminology for neonates. While NICE have published algorithms for the management and risk stratification of sepsis based on similar principles to the Sepsis-3 group, the age ranges are broad (0–5 years).[46] In addition, NICE guidance on antibiotic use in neonates uses the terms infection and sepsis interchangeably and does not discuss how sepsis should be defined.[47]

Infective organisms and microbiology

One of the most common criteria in diagnosing neonatal sepsis is the isolation of an infective organism. Blood and/or cerebrospinal fluid (CSF) culture is the most common method of isolating an infective organism. However, the ANZNN have added CSF polymerase chain reaction (PCR) into their criteria, likely in view of the high sensitivity and specificity of new PCR-based techniques in diagnosing infection.[5] NeonIN is the only network discussed that accepts suprapubic aspirate cultures as an indicator of urosepsis. Urine culture is not used by most definitions as the rate of neonatal urinary tract infection in EOS and in VLBW neonates is low,[48] suprapubic aspiration is invasive, and it is not routinely recommended in neonates with EOS by most expert bodies including the American Academy of Pediatrics.[49] In contrast, urine culture is likely to be of greater utility in evaluating LOS in premature neonates where approximately 11% may have evidence of urinary tract infection.[50]

The NICHD considers only bacterial and fungal pathogens cultured from blood and CSF in their definitions of neonatal sepsis.[17,51–63] The CDC classifies sepsis as bacterial isolation from any normally sterile site.[64] The ANZNN requires positive blood and/or CSF cultures or a positive PCR from CSF for diagnosis of sepsis.[65] Similar to many definitions, the ANZNN includes bacteria and fungi under the heading of sepsis but additionally provides specific criteria for the diagnosis of viral sepsis, which will not be discussed here. The VON criteria classify bacterial sepsis and meningitis together and require the isolation of pathogens from a prespecified list in either blood or CSF culture[66] for the diagnosis of EOS and LOS. Fungal sepsis is classified within the VON manual using the same diagnostic criteria as LOS except with isolation of a fungal pathogen rather than a bacterium.[66] NeonIN uses positive bacterial culture from blood, CSF or a suprapubic aspirate in the diagnosis of bacterial sepsis.[67] NeonIN diagnoses invasive fungal infection separately from bacterial, requiring only a positive culture from blood or CSF without any additional criteria.[68] Positive bacterial, fungal and viral cultures of blood and/or CSF are required in the Canadian Neonatal Network for the diagnosis of sepsis.[69,70] Both bacteria and fungi cultured from either blood or CSF are included in most definitions used in papers from the ASGNI.[71,72] NEO-KISS defines laboratory-confirmed bloodstream infection as isolation of bacteria from blood or CSF in addition to any two other criteria from a specified list of laboratory and/or clinical abnormalities.[73] In the case of bloodstream infection, the NEO-KISS guidance specifies that bloodstream infection must not be as a result of localised infection.[73]

The use of microbiological isolates for the diagnosis of sepsis is well established within neonatal literature. While identifying and treating the correct organism is essential, relying on microbiology testing alone to define sepsis has limitations. Blood cultures take hours to days to produce a definitive result[74,75] and therefore do not facilitate early diagnosis. In addition, reliance on microbiology in isolation does not help in identifying organ dysfunction, which is linked to adverse outcome in affected neonates[76] and has been a major focus of Sepsis-3.[22] While there is an important role for

microbiology results within the management of sepsis, current methodologies do not facilitate early recognition or screening of high-risk neonates. Newer "-omics" based technologies have potential to personalise the treatment of many diseases, including sepsis,[77] though at present these techniques remain experimental.

Duration of therapy

The intention to treat with ≥5 days of antibiotics is a common criterion for the diagnosis of sepsis in NICHD publications,[51,52,56–62] which specify that neonates either complete ≥5 days of antibiotics or die before the course is completed. The ANZNN requires antibiotics administration with therapeutic intent after the available clinical and laboratory evidence is considered, though a minimum duration of therapy is not specified. VON requires a prespecified duration of antibiotic therapy in the diagnosis of CONS sepsis but not in any other type of sepsis.[66] The NeonIN surveillance network requires the neonate receive ≥5 days of antibiotic therapy for a diagnosis of bacterial sepsis.[67] NEO-KISS requires a minimum duration of antibiotics only in the case of clinical sepsis where ≥5 days of therapy are needed.[73] The Canadian Neonatal Network require ≥5 days of antibiotic therapy in cases of clinical sepsis and in the diagnosis of primary bloodstream infection with organisms that might otherwise be considered contaminants.[70] ASGNI do not require a specified duration of therapy for sepsis diagnosis.

While duration of antimicrobial therapy is a common diagnostic criterion in research studies, this is usually in cases where sepsis was suspected but microbiological results were either negative or potentially difficult to interpret (e.g. CONS). While never explicitly discussed, the use of a minimum duration of therapy does not appear evidence based and the duration of therapy chosen (most commonly 5 days) is likely arbitrary. In addition, the duration of therapy can only be applied retrospectively and is influenced by local practice. Therefore, treatment duration may not reflect the severity of illness in the individual neonate and does not facilitate the early identification of sepsis.

Contaminants and polymicrobial cultures

Contamination of microbial culture in neonatology, i.e. the growth of a non-pathogenic organism that was introduced during sample collection or processing,[78] is most commonly caused by skin commensals. Polymicrobial cultures are defined by the presence of ≥2 organisms in specimens collected for microbiological culture. Classification of polymicrobial culture and culture of potential contaminants remains especially challenging in premature neonates where the developing immune system means that commensal organisms can potentially cause invasive infection and more than one organism may be causing clinical symptoms concurrently.

The NICHD specify the organisms that would be considered contaminants if isolated from blood and/or CSF.[17,51,53,54,56–63] However, one NICHD study considered cultures of these organisms positive in the setting of LOS if the neonates received ≥5 days of antibiotic therapy.[57] The ANZNN[65] discuss CONS as a potential contaminant but do not specify other organisms that should be considered contaminants. The Canadian Neonatal network provide examples of common skin contaminants and a list of organisms that are considered pathogenic.[70] NEO-KISS does not provide a list of contaminants but does provide a specific list of organisms that should be considered pathogenic if isolated.[73] VON, NeonIN and ASGNI do not provide lists of organisms considered to be contaminants.

The manner in which polymicrobial cultures are addressed varies among NICHD studies. One NICHD paper considered polymicrobial cultures positive in the setting of EOS if one organism was considered a true pathogen.[58] Weston et al. simply reported that if one or more bacterial organisms were isolated the culture was considered positive as long as the infecting organisms were not on a prespecified list of common contaminants.[53] Wynn et al. considered cultures with 3 organisms positive only if the neonate died within 72 h, whereas cultures with 2 organisms were excluded if at least one of the organisms was from a list of prespecified common contaminants.[51] The ANZNN state that growth of a mixed CONS or other skin flora is not sufficient for the diagnosis of sepsis, though polymicrobial cultures are not otherwise discussed.[65] Within VON and the CDC, multiple pathogens may be independently recorded, but polymicrobial cultures are not otherwise discussed.[66,79] The VON definition states that if a bacterial pathogen and CONS are isolated from the same culture during an episode of LOS, it is simply classified as LOS, not CONS.[66] The Canadian Neonatal Network suggest that ≥2 organisms on a single culture or from multiple cultures collected on the same day would usually be considered contaminants,[70] though neonates with multiple organisms on culture may still be diagnosed with sepsis.[69] ASGNI states that sepsis usually requires a pure growth of a single organism from either blood or CSF[80–82]; however, one publication stated that a pure growth of "at least one" organism constituted a positive culture though this was not discussed further within this paper.[71] In cases of potential contaminants, the diagnosis of sepsis may still be made if clinical signs are present along with at least one of a specified list of laboratory abnormalities.[71,80,81] Blood cultures that yielded more than one organism in ASGNI publications were generally considered contaminants.[80,81] Polymicrobial cultures are not discussed within NEO-KISS or NeonIN publications.

Premature neonates are at particularly high risk of sepsis secondary to commensal organisms[83] and are disproportionately affected by polymicrobial sepsis.[84] Therefore, being able to confidently differentiate these diagnoses from culture contaminants is an important consideration in the interpretation of blood culture results but does not necessarily facilitate earlier diagnosis of sepsis.

CONS sepsis

CONS are among the commonest contaminants of neonatal blood cultures. CONS are also the most common pathogens isolated in LOS, and CONS sepsis has been associated with adverse short- and long-term outcomes, including neurodevelopmental delay.[85] In the setting of premature neonates with LOS, the isolation of CONS is therefore considered clinically significant. However, owing to the frequency of CONS contamination, many publications discuss CONS separately and apply additional clinical or laboratory criteria to differentiate contamination from true CONS sepsis.

Where CONS sepsis was defined separately from other cases of sepsis within NICHD publications, it required additional criteria such as laboratory findings suggestive of infection[17,54,63] or clinical signs of sepsis[54] in addition to positive blood cultures. NICHD publications most commonly considered CONS as a contaminant when isolated in the setting of suspected EOS,[53,58] though one NICHD publication permitted the inclusion of CONS in EOS diagnosis if it was felt to represent a true infection based on the clinical course and additional laboratory testing.[54] Diagnosis of CONS sepsis by VON criteria requires signs of generalised infection, an intent to treat with ≥5 days of antibiotic therapy and isolation of CONS from any of the following sources: peripheral blood, central line, lumbar puncture, ventricular tap, or ventricular drain after day 3 of life.[66] NeonIN require a positive blood culture for CONS (timing unspecified) in addition to ≥5 days of appropriate therapy[67] in order to diagnose CONS sepsis. The NEO-KISS definition requires isolation of CONS from blood culture (peripheral or central line) in addition to one of the following abnormal laboratory tests in order to diagnose CONS sepsis: raised C-reactive protein (CRP), raised interleukin 6 or 8, high immature-to-total neutrophil ratio, platelets $<100 \times 10^9$/L, or white cells $<5 \times 10^9$/L.[73] Supplementary to this is the requirement to fulfil two of the defined clinical and/or laboratory criteria given[73] (Tables 3, 4).

The only ASGNI publication providing diagnostic criteria for CONS sepsis defined it as episodes of LOS in which CONS was isolated,[81] the same criteria used by the Canadian Neonatal Network.[69] CONS sepsis is not discussed separately in ANZNN publications.

CONS sepsis is an important clinical entity within neonatal sepsis due to the frequency with which it contributes to LOS in the premature population.[86] Similar to the discussion on contaminants and polymicrobial culture, CONS is not relevant to the early diagnosis or screening of sepsis but requires consideration when interpreting microbiological data in potentially septic neonates.

Timing of sepsis

Following an episode of LOS, approximately 21% of premature neonates will go on to have at least one further episode of LOS.[87] It is therefore important to be able to differentiate consecutive sepsis episodes clearly from one another. The NICHD have stated that if the same organism is identified after 10 days of appropriate therapy or if a different organism was cultured at any time, they are considered separate sepsis episodes.[56,59] The ANZNN states that if the same organism has been isolated from blood or CSF within the previous 14 days it is considered a repeat isolate rather than a new episode of sepsis.[65] Within NeonIN, organisms that are grown in repeat cultures are considered new episodes if there are ≥7 days between positive bacterial cultures, ≥10 days between positive CONS cultures and ≥14 days between positive fungal cultures.[67,68] Since 2018, NEO-KISS states that 14 days since the beginning of the previous infection and a clinically infection-free period are needed to make a new diagnosis of sepsis.[73] The Canadian Neonatal Network specify that isolation of the same pathogen ≥7 days after the initial positive culture or isolation of a new pathogen at any time is considered a separate infective episode.[70] The CDC and ASGNI do not address the time interval required for positive cultures to be considered separate infective episodes. The time interval between episodes is not a common consideration in neonatal sepsis literature. It is, however, pertinent to the discussion of neonatal sepsis as it impacts the number of sepsis cases diagnosed within a NICU and is therefore relevant when auditing performance and comparing outcomes between centres.

The time at which sepsis occurs is commonly used to differentiate vertically transmitted infection from that acquired postnatally and, in most cases, sepsis is classified as either "early" or "late". In some cases, the time cut-off refers to the time of culture collection while others specify that it is the time of symptom onset. The CDC define EOS as sepsis in neonates aged <7 days and LOS as sepsis in neonates aged ≥7 days.[64] The NICHD specify that a positive culture obtained ≤72 h of life is consistent with EOS, whereas positive cultures beyond this are LOS.[17,51–63] NEO-KISS does not use the standard terms "early" and "late" in relation to infections and instead ascribes any infection where symptoms occur beyond 72 h of life as potentially nosocomial.[88] VON uses a "day of life" cut-off[66] with EOS classified as sepsis on or before day 3 of life and LOS as sepsis beyond day 3 of life, a classification which has important implications depending on the time of day a neonate is delivered. The ANZNN definition classifies neonates with onset of symptoms <48 h as EOS and those with onset of symptoms ≥48 h as LOS.[65,89] Onset at 48 h is also used in both the NeonIN surveillance network and the Canadian Neonatal Network to differentiate EOS from LOS, with EOS representing a positive culture at ≤48 h and LOS a positive culture >48 h.[67,69] The differentiation of EOS and LOS within the ASGNI was also based on timing of ≤48 h (EOS) or >48 h (LOS).[71,80,82] Though it is not specifically noted whether this represents the timing of symptom onset or culture collection, there is mention within manuscripts that data on the timing of culture positivity was recorded, so presumably this was the reference point used.[80,81]

The use of EOS and LOS is well established in neonatal literature. The timing of onset is used to differentiate infections

Table 3. Laboratory test cut-offs used in the diagnosis of neonatal sepsis.

Organisation	Setting	CRP	White cell count	Full blood count	Platelet count	Immature:total white cell ratio	Base excess	Blood glucose	Interleukins 6 + 8
National Institute of Child Health and Human Development (NICHD)	Diagnosis of CONS sepsis only[17,54,59,63]	>1 mg/dL	Not discussed	Mentioned, values not specified	Not discussed	Not discussed	Not discussed	Not discussed	Not discussed
Australasian Study Group for Neonatal Infections (ASGNI)	Required to diagnose sepsis.[71,82] To differentiate potential contaminants from true sepsis only[80,81]	Mentioned, values not specified	$<4\times10^9$/L $>20\times10^9$/L	Not discussed	$<150\times10^9$/L	Immature WBC ≥20% total WBC	Not discussed	Not discussed	Not discussed
Neo-KISS	Diagnosis of clinical, laboratory-confirmed and CONS sepsis[73a]	>2 mg/dL	$<5\times10^9$/L	Not discussed	$<100\times10^9$/L	Immature neutrophils >20% total neutrophil count	BE <−10 mEq/L	>140 mg/dL	Mentioned, values not specified

CONS coagulase-negative staphylococcus, *CRP* C-reactive protein.
[a]I:T ratio, leucocyte count and platelet count are used in defining CONS sepsis only.

Table 4. Clinical criteria used in the definition of sepsis.

Organisation	Clinical criteria
National Institute of Child Health and Human Development (NICHD)[17,54,55]	Clinical signs required but not specified
Australian and New Zealand Neonatal Network (ANZNN)[65]	Clinical signs required but not specified
Canadian Neonatal Network[70]	Used in the diagnosis of primary blood stream infection and clinical sepsis Specific list provided: • fever (>38 °C), hypothermia (<37°C), apnoea, bradycardia, chills, hypotension
Australasian Study Group for Neonatal Infections (ASGNI)[71,80–82]	Diagnosis of sepsis requires clinical signs to be present Examples given: • Fever, Hypothermia, temperature instability, apnoea, bradycardia, increased oxygen requirement, feed intolerance, lethargy, hypotonia
Vermont Oxford Network (VON)[66]	Diagnosis of CONS sepsis requires clinical signs to be present Examples given: • Apnoea, temperature instability, feeding intolerance, worsening respiratory distress, hemodynamic instability
NEO-KISS[73]	One of the several possible criteria that may be used Specific list provided: • Fever, hypothermia or temperature instability, tachycardia, bradycardia or heart rate instability, new or more frequent apnoea, capillary refill time >2 s, skin colour, increased respiratory support, unstable clinical condition, apathy

which are vertically transmitted from those acquired postnatally as these both have distinct microbiological profiles [90] and prognosis. Differentiating EOS and LOS is important from not only a treatment perspective but is also a key consideration for the premature and VLBW populations as it allows collection of data on nosocomial infections, which is an important outcome measure in the care of premature neonates.

Clinical signs and culture negative sepsis

The presence of clinical signs is a common theme within the definitions of sepsis discussed, though not universal. Most publications including clinical signs in their diagnostic criteria provide no guidance on what specific signs should be considered pathological and do not use continuous vital sign monitoring. NEO-KISS and the Canadian Neonatal Network are the only networks to provide a prescriptive list of the clinical features that should be considered in a diagnosis of sepsis[70,73] (Table 4).

The inclusion of clinical signs as a criterion in the diagnosis of sepsis varied between NICHD publications with few studies including it in the diagnostic criteria and none of these studies specifying the signs they considered indicative of a diagnosis of sepsis.[17,54,55] The ANZNN definition requires the presence of a clinical picture consistent with sepsis but does not specify what clinical features should be present.[65] VON uses clinical signs of infection in the diagnosis of CONS sepsis and provides examples of some signs that may be present.[66] The Canadian Neonatal Network requires clinical signs of sepsis to be present as one of the criteria for both laboratory-confirmed bloodstream infection and clinical sepsis,[69,70] with specific signs listed. Clinical signs are required for the diagnosis of sepsis in ASGNI publications. These are not specified in some publications,[71,80] and while examples are provided in other texts[81,82] they state that it remains at the discretion of the clinician as to what signs are indicative of sepsis. NEO-KISS requires the inclusion of clinical criteria in the diagnosis of laboratory-confirmed CONS and clinical sepsis and provides a specific list of the clinical criteria that should be used.[73] Clinical signs of sepsis were not part of the diagnostic criteria for sepsis in the NeonIN surveillance network.[67]

NEO-KISS is one of the few organisations that lists a separate diagnosis of "clinical sepsis" and it is defined as follows: antibiotics required for ≥5 days, no infection at another site, and blood cultures are either negative or not obtained.[73] In addition, two criteria are required from a list of clinical and/or laboratory parameters listed for standard bloodstream infection. One NICHD publication on neurological follow-up of former premature neonates defined clinical sepsis as a diagnosis if ≥5 days of antibiotics were given to a neonate with a negative culture in the setting of LOS.[62] The Canadian Neonatal Network have specific criteria for the diagnosis of clinical sepsis requiring the presence of clinical signs, negative cultures, the absence of infection elsewhere, and ≥5 days of antibiotic therapy.[70] Separate diagnoses of clinical/culture-negative sepsis are not provided in the ANZNN, ASGNI, VON, CDC or NeonIN.

The use of clinical signs in the diagnosis of sepsis among neonates seems logical as alterations in clinical parameters are common early in the clinical course of neonates with fatal sepsis.[91] However, the early signs and symptoms vary greatly between cases and may be anywhere on a spectrum between non-specific presentations common to a variety of neonatal diseases and multiorgan dysfunction. Owing to the difficulties in accurately detecting neonatal sepsis clinically, there is increasing interest in the use of complex physiological data and continuous vital sign monitoring to detect and predict neonatal pathophysiology.[92] The use of big data analytics shows promise in neonatal sepsis but will require further validation before it can be adopted into routine practice.[92]

Laboratory data and biomarkers

Additional laboratory data beyond microbiological testing features in the diagnostic criteria of some organisations (Table 3). While the availability of infection biomarkers in neonatology is undoubtedly useful, care must be taken when they are used in defining sepsis. The cut-off values used for sepsis biomarkers are not universal and the use of different cut-offs has a considerable impact on the sensitivity and specificity of the results.[93] Many traditional biomarkers such as CRP may be normal early in sepsis, meaning that the positive and negative predictive value of such tests may differ depending on the time period during which they are measured and whether serial measurements are obtained.[94] In addition, laboratory values are affected by the particular assay used locally and therefore it may be more valuable to consider what the increase from baseline is, rather than the absolute value obtained.

Laboratory data other than microbiology culture in NICHD publications is used only in the diagnosis of potential CONS sepsis.[17,54,59,63] Where the results of laboratory tests are employed, they represent common haematological and biochemical investigations such as CRP and full blood count (FBC).[17,54,59,63] In some ASGNI studies, sepsis diagnosis required abnormal laboratory data in addition to positive blood/CSF cultures.[71,82] The abnormal laboratory data were clearly specified in one paper and included CRP or abnormal haematological data that would be readily available from FBC or blood smear,[71] though elsewhere laboratory tests were not specified.[82] In other ASGNI studies, additional haematological laboratory data were used only to differentiate potential contaminants from true sepsis.[80,81] Laboratory abnormalities may be used as part of the diagnostic criteria in the NEO-KISS definitions of laboratory confirmed, CONS and clinical sepsis.[73] NEO-KISS is the only organisation to include interleukins 6 and 8 in their laboratory criteria for neonatal sepsis. Interleukins 6 and 8 have been shown to rise more rapidly in neonatal sepsis than traditional biomarkers and have favourable sensitivity and specificity early in sepsis.[95] The Canadian Neonatal Network allow the use of antigen testing in the diagnosis of bloodstream infection, but this is not discussed further.[70] The ANZNN, VON, NeonIN and CDC do not include additional laboratory criteria beyond standard microbiological testing.

Though not discussed in the literature above, biomarkers may also have potential to help guide investigation and treatment in neonatal sepsis. NICE guidelines suggest that CRP values may be used to plan further investigations such as lumbar puncture and that trends in CRP values may help in deciding the duration of antimicrobials.[47] Transcriptomic, proteomic and metabolomic investigations have potential to revolutionise the diagnosis and treatment of neonatal sepsis.[96] However, these novel biomarkers have not been validated in the neonatal population, and existing studies are limited, among other things, by the heterogenous definitions of sepsis used by investigators.[96] Most of the work on neonatal biomarkers has traditionally focussed on examining biomarkers that may detect early inflammatory response to sepsis, rather than organ dysfunction. This contrasts with biomarkers used by Sepsis-3 in the SOFA score (creatinine, bilirubin and platelet count), which screen for the complications of sepsis, namely organ dysfunction, rather than trying to look for early rises in acute-phase reactants.[22] The Sepsis-3 group have also acknowledged that, while newer biomarkers of organ dysfunction are becoming available, they would require extensive validation before potential inclusion in future versions of the SOFA score.[22]

Subclassification of sepsis

Subclassification of sepsis is not a common theme though some networks classify meningitis separately or require specific criteria for its diagnosis. Cases of EOS and LOS were rarely subclassified within NICHD publications; however, one study included early-onset meningitis separately from EOS,[60] and another subclassified neonatal infection as clinical infection alone, EOS/LOS alone, sepsis and necrotising enterocolitis or meningitis with and without sepsis.[62] In some publications, CONS sepsis was subclassified into: "definite infection" if there were 2 positive blood cultures within 48 h or 1 positive blood culture with a raised CRP (>1 mg/dL), "possible infection" with 1 positive blood culture and a requirement of 5 days of antibiotic therapy, and "probable contaminant" with 1 positive blood culture without CRP rise and without antibiotic therapy of at least 5 days' duration.[17,59,63] Sepsis was not subclassified in ASGNI publications; however, meningitis had specific diagnostic criteria, requiring either a positive CSF culture or a positive blood culture in combination with a CSF white cell count $>100 \times 10^6$/L and a clinical picture consistent with the diagnosis.[71,80–82] In addition, one ASGNI paper on invasive fungal infection stated that fungal meningitis requires either a CSF white count of $>10^9$ in the setting of a positive blood culture or a positive CSF culture.[72]

The Canadian Neonatal Network have a separate diagnosis of central line-associated bloodstream infection that is diagnosed in neonates developing a bloodstream infection while a central line was in situ or within 2 days of removal of a central line.[69] Meningitis and ventriculitis were also classified separately in the Canadian Neonatal Network.[69,70] NEO-KISS subcategorises bloodstream infection if a central line was present at the time of infection or in the preceding 48 h.[73] Sepsis is not subclassified within the VON, CDC, NeonIN surveillance network or ANZNN publications, and none of the organisations discussed provide separate definitions for premature and term neonates.

DISCUSSION

At present, there is no universally accepted definition of neonatal sepsis. While common themes are present in much of the existing literature, the specific criteria used to define sepsis differ between organisations. The isolation of an infective organism from blood or CSF is one of the commonest criteria in current literature. The prominence of microbiological cultures in neonatal sepsis publications reflects the importance of accurately identifying the causative organism in guiding antimicrobial therapy.[5] Current literature also reflects the fact that while neonates, especially those born premature[83] and with complex medical diagnoses,[97] are at higher risk of polymicrobial sepsis and sepsis secondary to CONS, stricter diagnostic criteria are used to differentiate these episodes from simple blood culture contamination. The timing of sepsis is another important theme in current literature with many organisations differentiating between EOS and LOS based on the onset of symptoms or timing of positive culture collection. Dividing sepsis into EOS and LOS differentiates between vertical infections and those acquired postnatally and helps to tailor empirical therapy based on likely pathogens.[5] Accurately delineating the timing of infection relative to delivery is also important for defining nosocomial infections in the premature population where this is an important outcome measure of NICU performance. Treatment with ≥5 days of antibiotics is used as a criterion in some publications when defining cases of neonatal sepsis. While not evidence-based, treatment duration appears to be used in identifying cases where there was genuine clinical concern from those in which antibiotics were simply administered empirically. Clinical signs and laboratory data are often used as adjuncts to support sepsis diagnosis though they are not universal and rarely an absolute requirement. This reflects the fact that clinical presentation may be non-specific[5] and laboratory data unhelpful[94] early in neonatal sepsis. Lastly, there is a recognition that some subclassification is needed within neonatal sepsis, either because these subtypes influence prognosis[98] or because subclassification dictates the duration and choice of therapy.[99]

Many of the sepsis definitions currently used in neonatology have either developed organically over time or may be the result of expert consensus from smaller organisations and thus lack the extensive evidence base and peer review that has resulted in recent developments within the adult field.[22,30] For accuracy, the diagnosis of sepsis in neonatal literature is often retrospective, with a heavy focus on microbiological culture results. RCTs occupy a unique space within neonatal sepsis literature as they provide inclusion and exclusion criteria rather than strict definitions of sepsis in many cases. Owing to the differing study methodology and the volume of literature requiring discussion, RCTs have not been included within this manuscript. RCT definitions are, however, deserving of discussion elsewhere and will be addressed in a future publication from our group.

Giannoni et al. have found that among septic neonates it is those with septic shock, defined in this case as hypotension requiring catecholamine treatment, and requirement for mechanical ventilation who have higher mortality.[76] These findings suggest that, similar to adult patients, the presence of organ

dysfunction is an important contributor to adverse outcome and further highlights the need for both clearer guidance on the diagnosis of neonatal sepsis and the need for a robust screening tool to identify organ dysfunction in term and premature neonates. While the work of Sepsis-3 provides an excellent example of how we can approach the complex process of defining sepsis within neonatology, it is clear that the definitions and screening criteria produced by the Sepsis-3 initiative cannot be directly translated into neonatology. The foremost reason for this is that neonates and adults are very distinct patient populations and therefore the presentation, disease progression, diagnosis, treatment and outcomes of interest differ greatly between adults and neonates. In addition, many of the criteria which could be used in a screening tool for sepsis, such as thrombocytopaenia or renal failure, would themselves need evidence-based definitions and adjustments for use at the extremes of viability where medical evidence is most lacking. The clinical presentation within the neonatal population also differs from adults with many of the initial signs and symptoms being non-specific.[5] In addition, many of the laboratory investigations for sepsis in adults and older children have poor sensitivity and specificity in neonates or may be influenced by gestational age.[100] These factors make the inclusion of clinical signs and inflammatory markers challenging in a neonatal screening tool. The use of simple physiological parameters in neonates is also much more challenging than in an adult population. Normal ranges for vital signs and clinical parameters such as BP or heart rate differ based on gestational and postnatal age.[101] There is also increasing recognition that BP is not an adequate marker of perfusion in the premature neonate[102,103] and that objective measurement of systemic blood flow is required for the assessment of haemodynamic status. In addition, while many modalities are available for circulatory monitoring in neonatology, there is no current gold standard.[104] This has important implications for design of an organ dysfunction scoring system or sepsis screening tool that might be analogous to the SOFA or qSOFA scores, both of which utilise normal ranges for vital signs in adults.[22] In combination, these factors make the definition and diagnosis of septic shock much more complex in neonatology as this requires the identification of circulatory abnormalities for diagnosis as per Sepsis-3.[22]

Premature neonates are a unique cohort within neonatology, representing a large proportion of those presenting with sepsis,[105] and being at high risk of mortality following the onset of organ dysfunction.[106] Identifying sepsis in premature neonates is particularly challenging as clinical presentation is especially non-specific,[107] and immaturity of organ systems at birth means that baseline organ dysfunction may be present as a result of prematurity. This has implications for screening as several of the parameters used in the SOFA score are affected by lower gestation or birth weight, including degree of respiratory support,[108] hyperbilirubinaemia,[109] platelet count,[110] BP[111] and creatinine.[112] Even term neonates, in whom it should theoretically be easier to identify new-onset organ dysfunction, may have alterations of bilirubin[113] and creatinine levels for reasons other than sepsis.[114] In addition, very few of these laboratory investigation and physiological parameters have established normal ranges that account for the gestation or day of life, and it is recognised that some investigations such as creatinine may be affected by maternal or placental factors and therefore change considerably in the first days of life.[112] It may therefore be that changes in organ dysfunction or trends over time may be most important in complex patients, such as premature neonates or those with congenital abnormalities, who may have clinical or biochemical evidence of organ dysfunction at baseline related to their immaturity or underlying diagnosis. The timing of clinical or laboratory assessment may also be an important consideration to account for the potential effect of transitioning on screening tool results in at-risk neonates. While not designed as a tool for the definition of sepsis, the "Neonatal Early-Onset Sepsis Calculator" provides an excellent example of how accounting for the transitioning period in sepsis screening can be successfully achieved.[115] In this case, the authors allowed a window of 2 h after birth in which physiological abnormalities may be acceptable without necessarily having to adjust the risk of sepsis calculation. Such considerations are important not only for accuracy of diagnosis but also for antimicrobial stewardship and to avoid unnecessary escalation of care. Any neonatal-specific screening tool will therefore require either gestation-specific normal ranges to be established for each parameter used or will require screening criteria that will account for the unique physiological and biochemical status of term and premature neonates.

Neurological outcome is one of the most important metrics of neonatal care, and this is especially so in the premature population where survival without disability is strongly related to gestational age.[116] While adult neurological impairment is now recognised in older sepsis survivors,[117] it is not nearly as common or severe as in the neonatal population.[118] Long-term neurological outcome is therefore rarely available in adult sepsis studies with most focussing on short-term outcomes, such as survival. This is relevant to note as much of the recent data on Sepsis-3 definitions and screening tools relates only to short-term outcomes, such as validation, diagnostic accuracy and mortality.[119,120] As neonatologists, we are much more focussed on long-term outcome data, especially that relating to neurological outcome and organ dysfunction in ex-premature neonates surviving into childhood. The outcome data used to validate definitions in adults and neonates are therefore likely to be very different and neonates involved in early studies of any future consensus definitions will require long-term follow-up.

A unified definition of neonatal sepsis is important to improve practice, allow comparison of outcomes between centres, facilitate audit of best practice and improve the quality of clinical and experimental research in the area. However, replicating the work of Sepsis-3 within neonatology is inherently more complex, and the definitions and screening tools that are produced from any such consensus definition are likely to differ considerably from those produced by Sepsis-3. Furthermore, the validation of a consensus definition of neonatal sepsis would require not only short-term outcome data but also long-term follow-up to evaluate outcomes specific to neonatology. First, an evidence-based, validated consensus definition of neonatal sepsis is required for use within research and clinical practice. This will require the formation of an expert committee, systematic literature review and initiation of a Delphi process to identify criteria for the definition of neonatal sepsis. Second, a validated set of screening criteria are needed that account for the complex nature of sepsis presentation within the term and premature populations. Validation of any resulting definitions or screening criteria could first be performed retrospectively on existing data sets before being introduced into clinical practice on a prospective basis. Similar to the criteria of Sepsis-3, neonatal screening tools should be easy to use at the bedside, identify at-risk patients and should be validated against clinical outcomes. Standards of care in neonatal sepsis should also be established (e.g. time from screening to antibiotic delivery) to allow comparison of care between centres and facilitate maintenance of best practice. The resulting work could be incorporated into clinical initiatives similar to the Surviving Sepsis Campaign as well as providing clearer definitions for use in clinical and experimental work within the field.

CONCLUSIONS

Differing opinions on the true nature of neonatal sepsis have meant that multiple definitions of neonatal infection have evolved.[26] Although certain criteria are common between

definitions, there is a lack of consensus on parameters and cut-offs. The Sepsis-3 group have successfully developed and validated new, simplified definitions and screening criteria for sepsis that are based on the presence of organ dysfunction in adults with suspected infection. At present, definitions of neonatal sepsis in published literature are heterogenous with a heavy emphasis on microbiological results rather than organ dysfunction. A consensus definition of neonatal sepsis has considerable scope to improve the care of at-risk neonates and the work of Sepsis-3 provides a clear roadmap on how such a definition may be developed.

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ADDITIONAL INFORMATION

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