Clinical Practice Guidelines

Diagnosis and Management of Neonatal Sepsis

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EXECUTIVE SUMMARY

Neonatal sepsis is an important cause of morbidity and mortality. Globally, neonatal sepsis accounts for 8% of all neonatal deaths in the first week of life and 37% of all deaths from the 2nd to 4th weeks of life (1). In hospital settings, the incidence of culture proven neonatal sepsis is 16 per 1000 live births in India (2). A large study from a rural community in India reported 4 cases of culture proven neonatal sepsis per 1000 live births(3). Population-based studies from India report highly variable incidences of clinically suspected sepsis- ranging from 4.6 to 170 per 1000 live births (4).

The diagnosis and management of neonatal sepsis is one of the commonest challenges faced by Pediatricians in day-to-day clinical practice. Conventionally, neonatal sepsis is classified according to the time of onset as EONS (onset at <72 hours of life) and LONS (onset ≥ 72 hours of life), although this distinction is somewhat blurred in India and other developing countries (2). Based upon the localisation of sepsis, it can present as septicemia (bloodstream infection), pneumonia, meningitis, urinary tract infection etc. Fungal sepsis is also an important problem in India, particularly so among out born infants referred to tertiary care centres(5). Although neonatal sepsis is an important clinical and public health problem, there is a paucity of evidence-based guidelines for diagnosis and management. Moreover, guidelines for high income countries may not necessarily be applicable to low- and middle-income countries as the epidemiology of neonatal sepsis, the facilities for treatment and values and preferences may be quite different in these two settings. In view of the above, there is a felt need for evidence-based guidelines on the diagnosis and management of neonatal sepsis, with special reference to India and developing countries.

The guideline has been developed using standard methods adapted by the national neonatology forum in accordance with the process described in the GRADE handbook and WHO handbook for guideline development. The detailed methods are described elsewhere in this compilation of guidelines. Table below summarizes the recommendations for practice questions prioritized by the guideline panel in consultation with a wider group of NNF members.

SUMMARY OF RECOMMENDATIONS FOR DIAGNOSIS AND MANAGEMENT OF NEONATAL SEPSIS

S. No.	Recommendations	Strength of recommendations	Certainty of evidence
Diagnosis of neonatal sepsis			
1	a. The guidelines group suggests **NOT** to use serum CRP routinely for the diagnosis of sepsis in neonates with suspected late-onset sepsis	Weak	Moderate
	b. However, in level-2 neonatal units with no facilities for blood culture, the group suggests using serum CRP as a screening tool to *rule out* sepsis in neonates with a low probability of late-onset sepsis (for example, neonates with apnea, feed intolerance, or fast breathing)	Weak, context-specific	Not graded (Expert consensus*)
2	The guidelines group suggests that there is **NO** advantage in using PCT over CRP as a screening test for LONS.	Weak	Moderate
3	a. The guidelines group suggests using CSF WBC count and protein estimation for diagnosis in neonates being evaluated for suspected meningitis.	Weak	Moderate
	b. The group suggests **NOT** to use CSF glucose estimation for diagnosis in neonates being evaluated for suspected meningitis.	Weak	Low
Initiation of antibiotics for suspected early-onset sepsis			
4	The guidelines group suggests **NOT** using the various early-onset sepsis calculators (e.g., the EONS calculator by Kaiser Permanente network) developed in high-income countries for the management of well-appearing, asymptomatic neonates born at or after 35 weeks with risk factors for early onset sepsis&	Weak	Low
5	a. The guidelines group suggests administering antibiotics in *symptomatic*+ neonates born at any gestation *and* having maternal-perinatal risk factors¶ of early-onset sepsis.	Weak	Low#

	b. The guidelines group suggests considering initiation of antibiotic therapy in asymptomatic preterm neonates born before 35 weeks of gestation *and* having maternal-perinatal risk factors¶ of early-onset sepsis. In the > 32 weeks' gestation group, antibiotics may be considered for any one red flag risk factor or ≥2 yellow flag risk factors; and in the ≤32 weeks' gestation group for either one red or one yellow flag risk factor.	Weak	Not graded. (Expert consensus*)
	c.In case antibiotics are started, the guidelines group recommends that antibiotics may be stopped after 36 hours if the blood culture remain sterile, the baby's clinical condition remains stable, and there are no signs suggestive of sepsis.	Strong	Not graded (Expert consensus*)
6	For asymptomatic neonates born at or after 35 completed weeks of gestation and at risk¶ of early-onset sepsis, the guidelines group suggests administration of antibiotics *only* in the presence of positive laboratory markers of sepsis (such as, CRP, PCT or hematological parameters beyond age-appropriate cut-off values).	Weak	Low
Duration of antibiotics			
7	The guidelines group suggests **NOT** to use a shorter course of intravenous antibiotics (typically 5-7 days) in the management of neonates with uncomplicated@ and definite (i.e., culture-positive) neonatal sepsis; these neonates may preferably be treated with the standard course of antibiotics (typically 10-14 days).	Weak	Low
8	The guideline group suggests **NOT** to use a shorter course of antibiotics (typically 2-3 days) for the treatment of uncomplicated@ probable neonatal sepsis or pneumonia; these neonates may preferably be treated with the standard 5-7 days course of intravenous antibiotics.	Weak	Very low

9	The guidelines group suggests **NOT** to stop antibiotic therapy based on one or serial negative biomarker report(s) in neonates with uncomplicated@ probable (i.e., culture-negative) neonatal sepsis; these neonates may preferably be treated with the current standard practice of 5-7 days of intravenous antibiotics.	Weak	Very low
10	The guidelines group suggests **NOT** to use a short course of intravenous antibiotics (typically 14 days or less) in neonates with definite or probable uncomplicated$ neonatal meningitis; these neonates may preferably treated with the standard course of antibiotics (typically 21 days).	Weak	Very low
11	The guidelines group suggests **NOT** to use a shorter course of antibiotics (<4 weeks) in newborn infants with complicated meningitis (ventriculitis, brain abscess); these neonates may preferably be managed with the standard longer course of antibiotics (4-6 weeks).	Weak	Not graded (Expert consensus*)
12	The guidelines group suggests **NOT** to use a shorter course of antibiotics (typically ≤10 days) in newborn infants with uncomplicated% urinary tract infection (UTI); these neonates may preferably be treated using a standard longer course of antibiotics (typically 14 days)	Weak	Very Low
13	a. The guidelines group suggests using antifungal therapy for 14 days *after* documented clearance of Candida species from the bloodstream and resolution of signs attributable to candidemia (and **NOT** for a pre-fixed duration - typically 14-21 days).	Weak	Not graded (Expert consensus*)
	b. The group suggests a longer duration of antifungal therapy in case of a deep-seated tissue infection or metastatic complication based on the site of infection, the patient's response to treatment, and the resolution of signs and symptoms.	Weak	Not graded (Expert consensus*)

Choice of antibiotics in primary or secondary health-care settings			
14	The guidelines group suggests **NOT** to use Cefotaxime + Amikacin or higher broad-spectrum antibiotics for probable sepsis or meningitis in neonates *admitted to* special care neonatal units (*SNCUs*); these neonates may preferably be treated with the WHO recommended first-line antibiotics of Ampicillin + Gentamicin.	Weak	Very low

*No included studies

& We conditionally recommend use of EONS calculator by Kaiser Permanente network in select units where predominantly in-born neonates are treated and maternal Group B Streptococcus colonization is an important risk factor for EONS.

+ Clinical illness consisting of abnormal vitals such as: Tachycardia (Heart Rate≥ 160/min), Tachypnea (≥60/min), and/or Temperature instability (fever ≥ 100.4 degree C), supplemental oxygen requirement and/or need for continuous positive airway pressure, mechanical ventilation, or blood pressure support can be used as a predictor of early-onset infection. There is no evidence that hypoglycemia alone in an otherwise well-appearing infant is a risk factor for early onset sepsis. A newborn's clinical condition often evolves over initial hours after birth, and hence physician's discretion is advised to distinguish transitional symptoms from signs of clinical sepsis.

¶ Risk factors of early-onset sepsis

Red flag risk factors
Clinical diagnosis of Chorioamnionitis Fever – either ≥39.0°C once or 38.0°C to 38.9°C on two or more measurements 30 minutes apart without another clear source PLUS one or more of the following: (a) Baseline fetal heart rate >160 beats/min for ≥10 minutes, excluding accelerations, decelerations, and periods of marked variability, (b) Maternal white cell (WBC) count >15,000/mm^3 in the absence of corticosteroids and ideally showing a left shift, (c) Purulent-appearing fluid coming from the cervical os visualized by speculum examination.
Foul smelling Liquor
Other risk factors (Yellow flag risk factors)
Preterm premature rupture of membranes
Rupture of membranes for ≥ 18 hours
Intrapartum fever ≥ 38°C in presence of suspected or confirmed bacterial infection
Dai handling or unclean vaginal examination /delivery surface/cord tie

low certainty of evidence for no effect on mortality and lack of evidence on other critical outcomes in neonates born at or after 35 weeks of gestation and high certainty of evidence on one important outcome (antibiotic usage rates)

@ Uncomplicated sepsis defined as any condition that is NOT treated with more than 10-14 days of antibiotics as per current standards of care, eg., CNS infections, bone and joint infections, deep-seated abscesses

$ Uncomplicated meningitis defined as CNS infections that DOES NOT require more than 21 days of antibiotics as per current standards of care, eg. ventriculitis, cerebral abscess, subdural empyema

% Uncomplicated UTI defined as UTI WITHOUT anatomical abnormalities of kidney, ureters, urinary bladder, abscesses, pyonephrosis

INTRODUCTION

Neonatal sepsis is a clinical syndromic response mounted by a newborn infant towards an infection (6).Global burden as per literature is an estimated 1.3 million annual cases of neonatal sepsis worldwide leading to death of more than 2 lakh neonates annually (7). The neonates in LMICs are affected disproportionately due to poor maternal antenatal care, improper birthing facilities, overcrowding, lack of adequate equipment and professional health care providers (8). Neonatal Sepsis is further classified as per age of symptom onset into early (within first 72 hours of life) and late onset sepsis (after 72 hours of life) (9). This demarcation is not well defined in developing countries as recent studies have found that the organism profile, antimicrobial resistance pattern, important clinical presentation and their outcomes doesn't vary significantly amongst the two groups (5).

LMIC's, having one of the highest crude birth rates across the world, have been visualising improving rates of neonatal mortality. Hence the proportion of sick neonates being managed at level II and III neonatal care units have been increasing exponentially over the last decade due to improvement in basic infrastructure, equipment and training of health care professionals (10).However a significant improvement in Childhood mortality has not been paralleled by a similar reduction in neonatal mortality rate, which still contributes to 40% of the former (11).More so it is noteworthy that the developing world alone contributes towards 99% of this global burden of neonatal deaths(12). The rates of neonatal sepsis in developing world as per literature review vary between 49-170 per 1000 live births, with culture positive sepsis being 0.8-6.1/1000 live births and meningitis 0.8-6.1/1000 live births.(13) .Higher rates of neonatal sepsis in these regions can be attributed to lack of consensus definitions on neonatal sepsis and huge variability in management policies amongst various neonatal units for similar clinical scenarios (14). Henceforth there is an urgent need to formulate and disseminate national standardised guidelines for uniform evidence-based management of high-risk septic neonates.

SCOPE OF THE GUIDELINES AND TARGET AUDIENCE

Aim

The aim of these guidelines is to provide evidence-based guidance for key issues in the diagnosis and management of neonatal sepsis. The specific issues included in these guidelines are: (a) the diagnostic accuracy of the standard sepsis screen and of PCT versus sepsis screen for diagnosis of sepsis, of clinical scores for diagnosis of EONS, and of CSF cytochemistry for meningitis, (b) the optimal duration of systemic antibiotics for various situations in clinical practice- definite sepsis, probable sepsis, meningitis, ventriculitis, fungal sepsis, uncomplicated urinary tract infections, and duration guided by biomarker results, (c) the optimal time to start systemic antibiotics for asymptomatic neonates at risk for EONS- from birth or when symptoms develop or when lab tests are reported positive, and (d) the optimal antibiotic regimen for primary and secondary care, where culture sensitivity reports are not available.

Target audience

These guidelines are intended to be used by pediatricians who look after newborn infants at all levels of care, neonatologists, community health workers and other healthcare providers involved in the care of neonates. Moreover, the guidelines can be used by state and national health administrators, program managers and policymakers. The guidelines are expected to improve efforts in optimising the diagnosis of neonatal sepsis and the use of antimicrobials for treatment.

Population of interest

These guidelines are applicable to newborn infants being cared for in secondary (including special neonatal care units and district hospitals) and tertiary care (neonatal intensive care units) neonatal health facilities both in the public and private sector.

How to use these guidelines

This systematic review and GRADE approach led to the development of a set of 14 recommendations. Each recommendation was graded as **strong** when there was confidence that the benefits clearly outweigh the harms, or **weak** when the benefits probably outweigh the harms, but there was uncertainty about the trade-offs. A strong or weak recommendation was further classified as **conditional** if the benefits outweigh the harms in some situations but not in others. For example, some recommendations may be relevant only where certain types of facilities are available. To ensure that each recommendation is correctly understood and applied in practice, the context of all recommendations is clearly stated within each recommendation and additional remarks are provided wherever needed. Users of these guidelines should refer to these remarks, which are presented along with the evidence summaries within the guidelines.

QUESTIONS AND OUTCOMES

Process of selecting the questions

The guideline author panel included neonatologists working in tertiary care hospitals. A set of 29 questions and outcomes of interest were framed by the panel (See annexure 1 online). These sets of questions and outcomes were circulated to 49 pediatricians (including 15 consultants in the private sector, 15 consultants in the public sector, 7 neonatology trainees, 11 pediatric trainees and 1 miscellaneous) by a Google form. The questions were scored on a scale of importance and the top 14 questions were selected based upon the average of the responses. The outcomes were scored on a scale of 1 to 9 (7-9 of critical importance, 4-6 important and 1-3 not important).

Questions relevant to clinical practice

Based on the responses from the participants, the following list of questions were identified as being the most relevant to clinical practice:

Questions related to diagnosis of neonatal sepsis

1. Among newborn infants with clinically suspected LONS, do standard sepsis screens (combinations of CRP +/- Hematological parameters) have a high diagnostic accuracy for diagnosing LONS (defined by blood culture positive or PCR positive)?
2. Among newborn infants with clinically suspected LONS, do standard sepsis screens (combinations of CRP +/- Hematological parameters) have a higher diagnostic accuracy for diagnosing LONS (defined by blood culture positive or PCR positive) compared to Procalcitonin?
3. Among newborn infants with probable sepsis (symptomatic EONS or LONS), do CSF rapid diagnostic tests (abnormal CSF cytology and/or biochemistry individually & combinations) have a high diagnostic accuracy for diagnosing meningitis (defined by CSF culture or Gram stain or PCR)?

Questions related to initiation of antibiotics for suspected early-onset sepsis

4. Among ASYMPTOMATIC newborn infants delivered to mothers with one or more risk factors of EONS, do clinical sepsis scores (comprising maternal & infant risk factors) have a high diagnostic accuracy in diagnosing EONS (defined by culture or PCR)?

5. Among ASYMPTOMATIC newborn infants with maternal-infant risk factors of EONS, should antibiotics be administered immediately from birth rather than be administered once symptoms develop?
6. Among ASYMPTOMATIC newborn infants with maternal-infant risk factors of EONS, should antibiotics be administered immediately from birth rather than be administered once lab tests are positive?

Questions related to duration of antibiotics

7. Among newborn infants with definite uncomplicated sepsis (bloodstream infection), is a short course of antibiotics (typically 5-7 days) is noninferior to a standard course of antibiotics (typically 10-14 days)?
8. Among newborn infants with uncomplicated probable septicemia or pneumonia (culture negative), is a course of 2-3 days of intravenous antibiotics non-inferior compared to standard 5-7 days of intravenous antibiotics?
9. Among newborn infants with definite uncomplicated sepsis (bloodstream infection), is stoppage of intravenous antibiotics guided by biomarker turning negative (e.g. CRP, PCT) is non-inferior compared to a standard course of 10-14 days intravenous antibiotics?
10. Among Newborn infants with definite or probable meningitis, is a shorter course of antibiotics (typically 14 days) non-inferior to a standard course of antibiotics (typically 21 days)?
11. Among Newborn infants with complicated meningitis (ventriculitis, abscess), is a shorter course of antibiotics (typically <= 4 weeks) non-inferior compared to a standard course of antibiotics (typically 6 weeks)?
12. Among Newborn infants with uncomplicated UTI, is a shorter course of antibiotics (typically <= 10 days) non-inferior compared to a standard course of antibiotics (typically 14 days)?
13. Among Newborn infants with proven fungemia, is a fixed duration of anti-fungals (typically 14-21 days) non-inferior compared to at least 14 days anti-fungals after the last negative culture?

Question related to choice of antibiotics in primary or secondary health-care settings

14. Among Newborn infants in SNCU with probable sepsis/meningitis, is a combination of antibiotics Cefotaxime + Amikacin or higher superior compared to a standard course of Ampicillin plus Gentamicin?

Outcomes of interest

As mentioned above, the participants in the survey rated the outcomes as critical, important and neither critical nor important. The NNF suggested a list of standard critical and important neonatal outcomes that could be used across all questions and across all clinical practice guidelines being developed by several working groups. To ensure uniformity of outcomes, we modified the rating of the outcomes by the participants, while incorporating the suggestions of NNF. The final list of outcomes for the neonatal sepsis guidelines was as follows:

Critical

1. Mortality during hospital stay
2. Mortality within the 28 of life
3. Mortality by 12 months of corrected age
4. Relapse with culture-positive sepsis or meningitis
5. Relapse with culture-positive urinary tract infection (this was applicable only for question #13 above)

6. Moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant for control, cerebral palsy, cognitive disability, blindness or deafness)
7. Death or moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant for control, cerebral palsy, cognitive disability, blindness or deafness)
8. Seizures needing more than one anticonvulsant during follow-up (epilepsy) [this was applicable only for questions # 5 and #12 above]
9. Chronic renal failure (this was applicable only for question #13 above)
10. Hydrocephalus requiring surgical intervention (this was applicable only for questions #5 and #12 above)

Important

1. Duration of antibiotic therapy
2. Duration of hospital stay
3. Relapse with culture-negative (probable) sepsis or meningitis
4. Relapse with probable urinary tract infection (this was applicable only for question #13 above)
5. Serious adverse drug reactions
6. Cost of care

Neither critical nor important

1. Complications of sepsis (including shock, acute renal failure, MODS)
2. Complications of meningitis
3. Re-hospitalization within 6 months
4. Exposure to antibiotics
5. Any adverse drug reaction
6. Short-Term complications of urinary tract infections
7. Necrotising Enterocolitis

We performed a systematic review of literature and systematically extracted data from individual studies: study identifiers, setting, design, participants, sample size, intervention or diagnostic test, comparison group, outcome measures and results.

Interpretation of the recommendations

We used the GRADE approach for assessing the quality of evidence and the recommendations. The quality of the set of included studies reporting results for an outcome was graded as high, moderate, low or very low. The strength of recommendation reflects the degree of confidence that the desirable effects of adherence to a recommendation outweigh the undesirable effects. The decisions were made based on evidence of benefits and harms, quality of evidence, values and preferences of policymakers, healthcare providers and parents and whether the costs are qualitatively justifiable relative to the benefits in the settings in which the recommendations are to be implemented.

EVIDENCE REVIEW AND FORMULATION OF RECOMMENDATIONS

Search strategy

Search terms

We searched 3 databases: Pubmed, Embase and the CDSR. The panel had several group discussions and iterations before deciding on the search terms to be used. To ensure uniformity for all the questions, we arrive at a consensus for search terms related to "Intervention/diagnosis related terms", "sepsis/meningitis-related terms", "age-group related terms" and "study design related terms". Separate search terms were formulated for Pubmed, Embase and CDSR (see Annexure 2 online).

Search algorithm

The flowchart of the search strategy is shown in Annexure 3 online. In each database, we first searched for meta-analyses between 01/01/2018 and 30/06/2020. If a well conducted meta-analysis was found, it was directly used for the GRADE assessment.

If no meta-analysis was found in the above period, we searched for meta-analyses between 01/01/1990 and 31/12/2017. If a meta-analysis was found in this period, we found out the publication date of the latest study included in the meta-analysis. Then, we searched for RCTs or diagnostic studies (as applicable to the research question) for a time period starting after the date of the last published study until 30/06/2020. We also checked cross-references and "similar articles". We extracted data from the studies published after the meta-analysis and data from the individual studies included in the meta-analysis, entered the data into RevMan and conducted our own meta-analysis. This updated meta-analysis was used for entering data into GRADE.

If no meta-analysis was found between 01/01/1990 and 31/12/2017, we searched for individual RCTs or diagnostic studies (as applicable to the research question) from 01/01/1990 to 30/06/2020. We also checked cross-references and "similar articles". If more than one suitable study was found, we conducted our own meta-analysis in RevMan and used our meta-analysis for GRADE. If only one suitable study was found, the data was directly entered in GRADE.

If no meta-analysis or RCT or diagnostic study was found between 01/01/1990 to 30/06/2020, we repeated the search without terms for meta-analysis/RCT/diagnostic test for the above time period, to identify observational studies. If data in the form of 2 x 2 tables could be extracted from more than one observational study, we conducted our own meta-analysis of the observational studies and used the information in GRADE. If data in the form of 2 x 2 tables could be extracted from only one observational study, we directly used it in GRADE.

Data abstraction and summary tables of individual studies

A standardized form was used to extract information from relevant studies. Systematically extracted data included: study identifiers, setting, design, participants, sample size, intervention or exposure, control or comparison group, outcome measures and results. The following quality characteristics were recorded for RCTs: allocation concealment, blinding of intervention or observers, loss to follow up, intention to treat analysis, analysis adjusted for cluster randomization (the latter only for cluster RCTs). The quality characteristics recorded for observational studies were likelihood of reverse causality, selection bias and measurement bias, loss to follow-up and analysis adjusted for confounding. The studies were stratified according to the type of intervention or exposure, study design, birth weight and gestational age, where possible. Effects were expressed as RR or OR for categorical data, and as MD or WMD for continuous data where possible. All studies reporting on a critical outcome were summarized in a table of individual studies.

Pooled effects

We used pooled effects from the published systematic reviews, provided they were up to date and done appropriately. However, we pooled the data in RevMan 5 to perform fresh analysis if the published systematic review missed any relevant study, a new study became available after the publication of meta-analysis, or we identified a methodological problem with the meta-analysis. We used the author-reported adjusted effect sizes and CIs as far as possible for pooling the data. We used random effects models for meta-analysis if there was an important inconsistency in effects as the random effects model was not unduly affected by small studies. In case pooling of results was not possible, the recommendations were developed using the range of effect sizes observed in the individual studies.

Quality assessment

Quality assessment of the body of evidence for each outcome was performed using the GRADE approach. The GRADE approach was used for all the critical outcomes identified in the PICOs, and a GRADE profile was prepared for each quantitative outcome within each PICO. Accordingly, the quality of evidence for each outcome was rated as "high," "moderate," "low," or "very low" based on a set of criteria. As a baseline, RCTs provided "high-quality" evidence, while non-randomized trials and observational studies provided "low-quality" evidence. This baseline quality rating was then downgraded based on consideration of risk of bias, inconsistency, indirectness, imprecision, and publication bias. For observational studies, other considerations, such as magnitude of effect, could lead to upgrading of the rating if there were no limitations that indicated a need for downgrading.

Risk of bias

The standard Cochrane risk of bias tool was used. In studies where blinding was clearly impossible to implement (e.g. a shorter duration of antibiotics versus a standard duration), and the outcome being measured had no or negligible measurement bias (such as mortality), the studies were not downgraded for lack of blinding. If the outcome being measured had scope of measurement bias (such as "probable relapse"), the studies were downgraded for lack of blinding.

Inconsistency of the results

The similarity in the results for a given outcome was assessed by exploring the magnitude of differences in the direction and size of effects observed from different studies. The quality of evidence was not downgraded when the directions of the findings were similar and confidence limits overlapped, whereas quality was downgraded when the results were in different directions and confidence limits showed minimal overlap. If there was only one study, it was not downgraded for inconsistency.

Indirectness

Rating of the quality of evidence were downgraded where there were serious or very serious concerns regarding the directness of the evidence, i.e. where there were important differences between the research reported and the context for which the recommendations are being prepared. Such differences were related, for instance, to populations, interventions, comparisons, or outcomes.

Imprecision

The degree of uncertainty around the estimate of effect was assessed. As this was often a function of sample size and number of events, studies with relatively few participants or events (and thus wide confidence intervals around effect estimates) were downgraded for imprecision.

Publication bias

Quality rating could also be affected by perceived or statistical evidence of bias that may have led to underestimation or overestimation of the effect of an intervention because of selective publication based on study results. Where publication bias was strongly suspected, evidence was downgraded by one level. If the number of studies was too few to assess publication bias, they were not downgraded for publication bias.

GRADE profile software was used to construct "Summary of Findings" tables for each priority question; these tables include the assessments and judgements relating to the elements described above and the illustrative comparative risks for each outcome. Relevant information and data were extracted in a consistent manner from the systematic reviews relating to each priority question by applying the following procedures. First, up-to-date review documents and/or data (e.g. RevMan file) were obtained from the Cochrane Library. Secondly, analyses relevant to the critical outcomes were identified and selected. The data were then imported from the RevMan file (for Cochrane reviews) or manually entered into the GRADE profilers (for non-Cochrane reviews). For each outcome, GRADE assessment criteria (as described above) were applied to evaluate the quality of the evidence. In the final step of the assessment process, GRADE evidence profiles were generated for each priority question.

Formulation of recommendations

For each of the questions there were 2 reviewers and one senior supervisor. If the 2 reviewers were unable to have a consensus opinion, it was referred to the supervisor. Once the recommendations were made, they were discussed in detail in group meetings. Further inputs were sought, and draft recommendations were finalised. Wherever the guideline development panel required further clarifications, members of the NNF core committee for guideline development work were consulted. The formulation of recommendations was by building a consensus rather than Delphi method.

The process of consulting members of the NNF core committee did result in some changes in the wordings of recommendations for non-inferiority questions for which there was inadequate evidence in the literature to either support or refute the hypothesis. It was decided that for all such questions the recommendation would be voted as a weak recommendation against the intervention.

External review

Guidelines pertaining to each question were reviewed by 3 external reviewers (all Neonatologists of repute from tertiary care neonatal units both in the public and private sector) and by 1 editor from the NNF core committee (A methodologist with experience in GRADE recommendations). The external reviewers made open-ended suggestions and did not use a rating scale.

Changes suggested in the external review process were incorporated. In addition, an online meeting was held with all editors of the NNF core committee to sort out certain contentious issues. In summary, the changes suggested at various points of time in the review process included modification of criteria used for downgrading the evidence in case of lack of blinding where blinding was not possible and the outcome had no measurement bias, for downgrading evidence for inconsistency where there was only one trial, for downgrading for publication bias where there were too few trials to assess publication bias, changing the wording of the recommendations in case of non-inferiority hypotheses as mentioned above etc.

QUESTIONS, EVIDENCE SUMMARIES AND RECOMMENDATIONS

***Practice Question 1*: Among neonates with clinically suspected LONS, should CRP be used to screen for LONS (defined as culture positive)?**

PICO question

P= newborn infants
I= standard sepsis screen by CRP
C= blood culture
O= diagnostic accuracy for diagnosing LONS in newborn infants

Summary of evidence

Table 1 depicts the summary of findings.

Table 1: Summary of findings
Patient or population: newborn infants
Setting: all
New test: CRP **Reference test:** Blood Culture
Pooled sensitivity standard sepsis screen by CRP: 0.62 (95% CI: 0.50 to 0.72) | **Median specificity standard sepsis screen by CRP:** 0.74

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 20% Typically seen in	**Prevalence 40%** Typically seen in	**Prevalence 60%** Typically seen in		
	Standard sepsis screen by CRP	**Standard sepsis screen by CRP**	**Standard sepsis screen by CRP**		
True positives	**124** (100 to 144) **124 more TP in standard sepsis screen by CRP**	**248** (200 to 288) **248 more TP in standard sepsis screen by CRP**	**372** (300 to 432) **372 more TP in standard sepsis screen by CRP**	788 (22)	⊕⊕⊕◯ **MODERATE** [1,a]
False negatives	**76** (56 to 100) **124 fewer FN in standard sepsis screen by CRP**	**152** (112 to 200) **248 fewer FN in standard sepsis screen by CRP**	**228** (168 to 300) **372 fewer FN in standard sepsis screen by CRP**		
True negatives	**592** (- to -) [b] **592 more TN in standard sepsis screen by CRP**	**444** (- to -)[b] **444 more TN in standard sepsis screen by CRP**	**296** (- to -)[b] **296 more TN in standard sepsis screen by CRP**	1467 (22)	⊕⊕⊕◯ **MODERATE** [a]
False positives	**208** (- to -) [b] **592 fewer FP in standard sepsis screen by CRP**	**156** (- to -)[b] **444 fewer FP in standard sepsis screen by CRP**	**104** (- to -)[b] **296 fewer FP in standard sepsis screen by CRP**		

CI: Confidence interval
Explanations
a. Large variations in sensitivity and specificity across studies
b. 95% CI interval are left blank in brackets as these values are calculated for a median specificity of 0.74

Summary of judgements

Problem (is the problem a priority?)

Judgement: yes

LONS (sepsis occurring >72 hours after birth) is one of the most common serious complications associated with intensive care for newborn infants (15).Premature and low birth weight infants with LONS are at higher risk of mortality, morbidity, and need for intensive care support along with the need for prolonged hospitalization (16). LONS is associated with adverse neurodevelopmental outcomes, including cognitive impairments, cerebral palsy, visual, and hearing impairments (17).Clinical signs of infection in neonates can be nonspecific, and the diagnosis of LONS can be delayed if these signs are missed. The results of the microbiological culture of a potentially pathogenic organism from a blood sample takes about 24 to 72 hours. Delaying treatment of LONS may increase the risk of mortality and morbidity in newborn infants. However, empirical treatment of all infants with suspected LONS will result in the administration of unnecessary therapy (18). Indiscriminate use of antibiotics may lead to the emergence of drug resistance (19-24).

A variety of biomarkers have been proposed as tests to support the diagnosis of LONS (25, 26).When used in conjunction with blood culture, these biomarkers have the potential to suggest whether the infection is less or more likely in clinically suspected LONS. The universally used biomarker across the world in the diagnosis of LONS is CRP. CRP is an acute-phase reactant synthesized by liver cells in response to inflammation (27).CRP might be a potentially useful biomarker for diagnosing LONS (28-33).

Test accuracy (how accurate is the test?

Judgement: inaccurate

Overall, 2255 infants were included from 22 studies in this systematic review and meta-analysis. Participants in most studies were preterm or very low birth weight infants. Most studies used a pre-specified cut-off value for CRP (5-10 mg/L) for index test and identification of pathogenic microorganisms from blood culture as a reference standard. The risk of bias was low with an independent assessment of index and reference tests. At the median specificity of 0.74, pooled sensitivity was 0.62 (95%CI, 0.50-0.72).

Diagnostic accuracy of CRP at 20% prevalence of LONS was found to be 71.60% (95% CI 68.69 -74.38).

Diagnostic accuracy of CRP at 40% prevalence of LONS was found to be 69.20% (95% CI 66.24 - 72.05).

Diagnostic accuracy of CRP at 60% prevalence of LONS was found to be 66.80% (95% CI 63.78 - 69.72).

Evaluating a serum CRP level at the assessment of an infant with a 40% pre-test probability (the median of the included studies) of LONS generates a post-test probability of 26% for the negative test result and 61% for a positive test result. Therefore, it can be interpreted that determining the CRP level at the time of initial evaluation of LONS is unlikely to aid in early diagnosis of LONS or to select infants to undergo further investigations or treatment with antimicrobial or other supportive therapy.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: trivial

The desirable downstream clinical consequences of correctly treating true-positive cases include a decrease in the risk of mortality and morbidities like neurodevelopmental impairment (cerebral palsy, cognitive disability, blindness, or deafness). The desirable downstream clinical

consequences of correctly not treating true-negative cases include a decrease in the proportion of infants exposed to antibiotics, a decrease in the cost of care, and a decrease in the risk of antimicrobial resistance.

Diagnostic test RCTs that assessed downstream desirable effects in newborns that compared serum CRP (index test) with blood culture (reference standard) for the screening of LONS are not available. In clinical practice, most newborn infants with suspected LONS are likely to be initiated on antibiotic therapy after collecting sepsis screen (CRP) and blood culture. The desirable effects, therefore, are likely to be trivial.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: large

The undesirable downstream clinical consequences of incorrectly treating false-positive cases include; increase in the proportion of neonates on antibiotics, increase in the cost of care. and increased risk of antimicrobial resistance. The undesirable downstream consequences of not treating false-negative cases of LONS include an increase in the risk of mortality and neurodevelopmental impairment.

Diagnostic test RCTs that assessed downstream undesirable effects in newborns that compared serum CRP (index test) with blood culture (reference standard) for the screening of LONS are not available. Incorrectly treating false positives and incorrectly not treating false negatives cases of LONS is likely to have large undesirable effects.

Certainty of the evidence of test accuracy (What is the overall certainty of the evidence of test accuracy?

Judgement: moderate

The overall certainty of the evidence was moderate.

The risk of bias was low with an independent assessment of index and reference tests. At the median specificity of 0.74, pooled sensitivity was 0.62 (95%CI, 0.50-0.72).

At an estimated prevalence rate of 20%, for the LONS, the accuracy of the CRP test is estimated to be 71.60% (95%CI 68.69 to 74.38).

At an estimated prevalence rate of 40%, for the LONS, the accuracy of the CRP test is estimated to be 69.20% (95%CI 66.24 to 72.05).

At an estimated prevalence rate of 60%, for the LONS, the accuracy of the CRP test is estimated to be 66.80% (95%CI 63.78 to 69.72).

Certainty of the evidence of the test's effects (What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?)

Judgement: no included studies

Not possible to assess due to the lack of diagnostic RCTs. Diagnostic test RCTs that have compared serum CRP (index test) with blood culture (reference standard) for the screening of LONS are not available.

Certainty of the evidence of management's effects (What is the overall certainty of the evidence of effects of the management that is guided by the test results?)

Judgement: no included studies

Not possible to assess due to the lack of diagnostic RCTs. Diagnostic test RCTs that have compared serum CRP (index test) with blood culture (reference standard) for the screening of LONS are not available.

Certainty of the evidence of test result/management (How certain is the link between test results and management decisions?)

Judgement: no included studies

Not possible to assess due to the lack of diagnostic RCTs. Diagnostic test RCTs that have compared serum CRP (index test) with blood culture (reference standard) for the screening of LONS are not available.

Certainty of effects (What is the overall certainty of the evidence of effects of the test?)

Judgement: no included studies

Not possible to assess due to the lack of diagnostic RCTs. Diagnostic test RCTs that have compared serum CRP (index test) with blood culture (reference standard) for the screening of LONS are not available.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: No important uncertainty or variability

Indirect downstream consequences of treating false positive and not treating false-negative index test compared to reference standard: Mortality before discharge from hospital; Mortality by day 28 of life; Mortality by 12 months of corrected age; Duration of antibiotic therapy; Duration of hospital stay; Moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness); Death or moderate or severe neurodevelopmental impairment at or after 12 months of age.

As guideline authors, we are of the viewpoint that all the above-mentioned important outcomes of this guideline are valued highly by all the stakeholders including patients, families, clinicians, policymakers, and the legal system. Therefore, we do not consider that there is any important uncertainty about the importance of these outcomes.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: varies

The microbiological blood culture remains the standard for the diagnosis of LONS. However, in settings where an option of performing blood culture is not available and a serum CRP level can be evaluated is a viable alternative. However, the limitations of the false positive and false negative tests should always be kept in mind.

Resources required (*How large are the resources required?)*

Judgement: moderate costs

No studies are available that compared the cost of different approaches (CRP versus blood culture) for the screening of LONS. The cost incurred in the purchase of the CRP test kit is likely to be lower. Qualitative CRP can be performed at the bedside as a point of care test. Pathology technicians would be required to perform a quantitative laboratory-based CRP test. The cost incurred in purchasing automated blood culture systems is likely to be higher. A microbiologist/ pathologist lead microbiological culture also has a human resource cost associated with training and salary.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: No included studies as no eligible studies were available.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: No included studies

Although no studies are available, the availability of a serum CRP test is likely to improve the screening of LONS in SNCU settings. It is expected that most tertiary care settings will have a microbiological laboratory that conducts blood culture through traditional or automated techniques.

Equity (what would be the impact on health equity?)

Judgement: Probably increased

Although no studies are available, the availability of a serum CRP test is likely to improve the screening of LONS in SNCU settings. It is expected that most tertiary care settings will have a microbiological laboratory that conducts blood culture by traditional or automated techniques.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: Probably yes

There is no evidence against the acceptability of serum CRP based screening for diagnosis of LONS. CRP is the most widely used diagnostic screening test in India and worldwide

Feasibility (is the intervention feasible to implement?)

Judgement: Probably yes

Although no studies are available, CRP screening in diagnosis of LONS can be made available without major difficulties where blood culture cannot be performed.

RECOMMENDATION

1a. The guidelines group suggests NOT to use serum CRP routinely for the diagnosis of sepsis in neonates with suspected late-onset sepsis

Weak recommendation, Moderate certainty of evidence

1b. However, in level-2 neonatal units with no facilities for blood culture, the group suggests using serum CRP as a screening tool to *rule out* sepsis in neonates with a low probability of late-onset sepsis (for example, neonates with apnea, feed intolerance, or fast breathing)

Weak context-specific recommendation, Not graded (Expert consensus)

Justification

Overall justification

Serum CRP has limited accuracy over blood culture in the diagnosis of LONS. It is unlikely to aid in the early correct diagnosis of LONS and treatment with antibiotics.

It may, however, be considered as a screening tool to rule out sepsis in neonates with a low risk of late-onset sepsis (for example, neonates with apnea, feed intolerance, or fast breathing) admitted to level-2 neonatal units with no facilities for blood culture.

Detailed justification

Test accuracy

Evaluating a serum CRP level at the assessment of an infant with a 40% pre-test probability (the median of the included studies) of LONS generates a post-test probability of 26% for the negative test result and 61% for a positive test result. Evaluating a serum CRP level at the assessment of an infant with a 20% pre-test probability of LONS generates a post-test probability of 11% for the negative test result and 37% for a positive test result. Evaluating a serum CRP level at the assessment of an infant with a 60% pre-test probability of LONS generates a post-test probability of 44% for the negative test result and 78% for a positive test result. Therefore, it can be interpreted that determining the CRP level at the time of initial evaluation of LONS is unlikely to aid in early diagnosis of LONS or to select infants to undergo further investigations or treatment with antimicrobial or other supportive therapy.

Subgroup Consideration

Additional data is required on the utility of CRP over blood culture from low and low-middle-income countries like India.

Implementation consideration

Efforts need to be made by health policymakers to make the reference standard blood culture test available in all settings wherever a newborn infant with LONS is assessed and treated.

Monitoring and evaluation

Wherever a newborn infant with clinically suspected LONS is tested by using a serum CRP screening test instead of blood culture, close clinical monitoring for potential complications and early referral to a higher centre is warranted.

Research priorities

There is an urgent need to investigate for a biomarker that is valid, accurate (accurately predicts presence or absence of infection), reliable (reproducible), simple to perform, one which gives results rapidly, easily available, and economical, for early diagnosis of LONS in newborn infants as an alternative to the traditional reference standard blood culture.

***Practice Question 2*: Among newborn infants with clinically suspected sepsis, should screening be performed by CRP or by procalcitonin to diagnose LONS (defined as culture positive)?**

PICO question

P= newborn infants ; I= standard sepsis screen by CRP; C= procalcitonin ; Reference standard = blood culture; O= diagnostic accuracy for diagnosing LONS in newborn infants

Summary of evidence

Table 2 depicts the summary of findings.

Table 2: Summary of findings

Patient or population: newborn infants ; **Setting:** all

New test: procalcitonin **Reference test**: blood culture

Pooled sensitivity standard screen by CRP: 0.71 (95% CI: 0.63 to 0.78) | **Pooled specificity standard screen by CRP** : 0.88 (95% CI: 0.80 to 0.93)

Pooled sensitivity procalcitonin: 0.85 (95% CI: 0.79 to 0.89) | **Pooled specificity procalcitonin:** 0.84 (95% CI: 0.78 to 0.89)

Test result	Number of results per 1,000 patients tested (95% CI)						Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 20% Typically seen in		**Prevalence 40%** Typically seen in		**Prevalence 60%** Typically seen in			
	standard screen by CRP	procalcitonin	standard screen by CRP	procalcitonin	standard screen by CRP	procalcitonin		
True positives	**142** (126 to 156)	**170** (158 to 178)	**284** (252 to 312)	**340** (316 to 356)	**426** (378 to 468)	**510** (474 to 534)	1038 (22)	⊕⊕⊕◯ **MODERATE** [1,a,b,c]
	28 fewer TP in standard screen by CRP		**56 fewer TP in standard screen by CRP**		**84 fewer TP in standard screen by CRP**			
False negatives	**58** (44 to 74)	**30** (22 to 42)	**116** (88 to 148)	**60** (44 to 84)	**174** (132 to 222)	**90** (66 to 126)		
	28 more FN in standard screen by CRP		**56 more FN in standard screen by CRP**		**84 more FN in standard screen by CRP**			
True negatives	**704** (640 to 744)	**672** (624 to 712)	**528** (480 to 558)	**504** (468 to 534)	**352** (320 to 372)	**336** (312 to 356)	1160 (22)	⊕⊕⊕◯ **MODERATE** [1,b]
	32 more TN in standard screen by CRP		**24 more TN in standard screen by CRP**		**16 more TN in standard screen by CRP**			
False positives	**96** (56 to 160)	**128** (88 to 176)	**72** (42 to 120)	**96** (66 to 132)	**48** (28 to 80)	**64** (44 to 88)		
	32 fewer FP in standard screen by CRP		**24 fewer FP in standard screen by CRP**		**16 fewer FP in standard screen by CRP**			

CI: Confidence interval

Explanations

a. In terms of the risk of bias, of the 22 studies included in our meta-analysis, 12 studies had an unclear bias in patient selection,13 studies were judged as having a low bias in the index tests, 21 studies were allocated as having a low bias in terms of reference standards, and 20 studies were judged as having a low bias in terms of flow and timing. In terms

of applicability concerns, 3 studies had a high bias in patient selection, 17 studies were judged as having a low bias concerning index tests, and 21 studies were classified as causing low concern about reference standards
b. Large I^2 values; CRP I^2 values for sensitivity 83.15, specificity 88.41; Procalcitonin I^2 values for sensitivity 79.20, specificity 86.73. Q test values for all <0.01
c. Five studies included newborn infants with LONS; three studies included newborn infants with early-onset neonatal sepsis (EONS), the remaining 16 studies included newborn infants with EONS and LONS or did not provide this information.

Summary of judgements

Problem (is the problem a priority?)

Judgement: yes

Late-onset neonatal sepsis infection (LONS: sepsis occurring >72 hours after birth) is one of the most common serious complications associated with intensive care for newborn infants (15) .Premature and low birth weight infants with LONS are at higher risk of mortality, morbidity, and need for intensive care support along with the need for prolonged hospitalization (16).LONS is associated with adverse neurodevelopmental outcomes, including cognitive impairments, cerebral palsy, visual, and hearing impairments (17, 34).

Clinical signs of infection in neonates can be nonspecific, and the diagnosis of LONS can be delayed if these signs are missed. The results of the microbiological culture of a potentially pathogenic organism from a blood sample takes about 24 to 72 hours. Delaying treatment of LONS may increase the risk of mortality and morbidity in newborn infants. However, empirical treatment of all infants with suspected LONS will result in the administration of unnecessary therapy (18) . Indiscriminate use of antibiotics may lead to the emergence of drug resistance (19-24).

A variety of biomarkers have been proposed as tests to support the diagnosis of LONS (25, 26). When used in conjunction with blood culture, these biomarkers have the potential to suggest whether the infection is less or more likely in clinically suspected LONS. The commonly used biomarkers for diagnosis of LONS include CRP and procalcitonin (35) . Procalcitonin (PCT) appears to be promising among the various biomarkers evaluated in the diagnosis of sepsis (31, 32, 36-42) . PCT is a precursor protein produced by monocytes and hepatocytes. Once exposed to bacterial endotoxin, PCT levels rise sharply within 2–4 h, each plateau within 6– 8 h, and then they return to normal levels after 24 h (43, 44) .Serum CRP levels may be increased in non-infective inflammatory conditions. Serum PCT levels appear to correlate with the severity of the microbial attack and rapidly decrease after appropriate antibiotic treatment. Therefore, it is important to evaluate which of the two biomarkers amongst CRP and PCT is more accurate in the diagnosis of LONS.

Test accuracy (how accurate is the test?

Judgement: inaccurate

Overall, 22 studies have compared CRP with PCT in neonatal sepsis. There were 2198 newborn infants (1038 with sepsis and 1160 with no sepsis). The reference standard for diagnosis was blood culture. Five studies included newborn infants with LONS; three studies included newborn infants with early-onset neonatal sepsis (EONS), the remaining 16 studies included newborn infants with EONS and LONS or did not provide this information. Ten studies were prospective cohort studies, 3 were cross-sectional and 9 were case-control type of studies.

In this question, we were comparing the performance of two tests, CRP and procalcitonin against each other, vis-a-vis their performance against a reference standard.
For CRP pooled sensitivity value was 0.71 (95% CI 0.63, 0.78) and pooled specificity was 0.88 (95% CI 0.80, 0.93).

For PCT pooled sensitivity value was 0.85 (95% CI 0.79, 0.89) and pooled specificity was 0.84 (95% CI 0.78, 0.89).
Accuracy of CRP at 20% prevalence rate of LONS was 84.60% (95% CI 82.21, 86.78)
Accuracy of PCT 20% prevalence rate of LONS was 84.20% (95% CI 81.79, 86.41)
Accuracy of CRP at 40% prevalence rate of LONS was 81.20% (95% CI 78.64, 83.58)
Accuracy of PCT 40% prevalence rate of LONS was 84.40% (95% CI 82.00, 86.60)
Accuracy of CRP at 60% prevalence rate of LONS was 77.80% (95% CI 75.09, 80.34)
Accuracy of PCT 60% prevalence rate of LONS was 84.60% (95% CI 82.21, 86.78)
From the above data, it can be interpreted that both the tests (CRP and PCT) were not sufficiently accurate in the diagnosis of LONS in newborn infants. In addition, when the prevalence of LONS is lower, both tests have similar accuracy. However, as the prevalence of LONS increases, the PCT test appears to be slightly more accurate than the CRP test.
Additional serious considerations apart from accuracy data regarding these screening tests are: CRP test is easily available and relatively less expensive. PCT test is not easily available and relatively more expensive.

Desirable outcomes (how substantial are the desirable anticipated effects?)
Judgement: small

The desirable downstream clinical consequences of correctly treating true-positive cases include a decrease in the risk of mortality and morbidities like neurodevelopmental impairment (cerebral palsy, cognitive disability, blindness, or deafness). The desirable downstream clinical consequences of correctly not treating true-negative cases include a decrease in the proportion of infants exposed to antibiotics, a decrease in the cost of care, and a decrease in the risk of antimicrobial resistance. Diagnostic test RCTs that have compared serum CRP and PCT (index tests) with blood culture (reference standard) for the screening of LONS and its downstream consequences are not available.

At a 20 % prevalence of LONS, there would be 28 fewer true positives and 32 more true negatives per 1000 subjects when screened by CRP versus PCT.
At a 40 % prevalence of LONS, there would be 56 fewer true positives and 24 more true negatives per 1000 subjects when screened by CRP versus PCT.
At a 60 % prevalence of LONS, there would be 84 fewer true positives and 16 more true negatives per 1000 subjects when screened by CRP versus PCT.
At a lower prevalence of LONS, the downstream desirable consequences of correctly treating and correctly not treating by using PCT instead of CRP appear trivial. to small. However, at the higher prevalence of LONS, the downstream desirable consequences of correctly treating and correctly not treating by using PCT instead of CRP appear small to moderate.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)
Judgement: large

The undesirable downstream clinical consequences of incorrectly (wrongly) treating false-positive cases include; increase in the proportion of neonates on antibiotics, increase in the cost of care and increased risk of antimicrobial resistance. The undesirable downstream consequences of incorrectly (wrongly) not treating false-negative cases of LONS include an increase in the risk of mortality and neurodevelopmental impairment.

Diagnostic test RCTs that have compared serum CRP and PCT (index tests) with blood culture (reference standard) for the screening of LONS and its downstream consequences are not available.
At a 20 % prevalence of LONS, there would be 32 fewer false positives and 28 more false negatives per 1000 subjects when screened by CRP versus PCT.

At a 40 % prevalence of LONS, there would be 24 fewer false positives and 56 more false negatives per 1000 subjects when screened by CRP versus PCT.
At a 60 % prevalence of LONS, there would be 16 fewer false positives and 84 more false negatives per 1000 subjects when screened by CRP versus PCT.
At a lower prevalence of LONS, the downstream undesirable consequences of incorrectly treating and incorrectly not treating by using PCT instead of CRP appear to be small. However, at the higher prevalence of LONS, the downstream undesirable consequences of incorrectly treating and incorrectly not treating by using PCT instead of CRP appear to be large.

Certainty of the evidence of test accuracy (What is the overall certainty of the evidence of test accuracy?
Judgement: moderate
The overall certainty of the evidence was moderate.
The risk of bias was low with an independent assessment of index and reference tests.
For CRP pooled sensitivity value was 0.71 (95% CI 0.63, 0.78) and pooled specificity was 0.88 (95% CI 0.80, 0.93).
For PCT pooled sensitivity value was 0.85 (95% CI 0.79, 0.89) and pooled specificity was 0.84 (95% CI 0.78, 0.89).

Certainty of the evidence of test's effects (What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?)
Judgement: No included studies
Not possible to assess due to the lack of diagnostic RCTs. Diagnostic test RCTs that have compared serum CRP and PCT (index tests) with blood culture (reference standard) for the screening of LONS are not available.

Certainty of the evidence of management's effects (What is the overall certainty of the evidence of effects of the management that is guided by the test results?)
Judgement: No included studies
Not possible to assess due to the lack of diagnostic RCTs. Diagnostic test RCTs that have compared serum CRP and PCT (index tests) with blood culture (reference standard) for the screening of LONS are not available.

Certainty of the evidence of test result/management (How certain is the link between test results and management decisions?)
Judgement: No included studies
Not possible to assess due to the lack of diagnostic RCTs. Diagnostic test RCTs that have compared serum CRP and PCT (index tests) with blood culture (reference standard) for the screening of LONS are not available.

Certainty of effects (What is the overall certainty of the evidence of effects of the test?)
Judgement: No included studies
Not possible to assess due to the lack of diagnostic RCTs. Diagnostic test RCTs that have compared serum CRP and PCT (index tests) with blood culture (reference standard) for the screening of LONS are not available.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)
Judgement: No important uncertainty or variability

Indirect downstream consequences of treating false positive and not treating false-negative index test compared to reference standard: mortality before discharge from hospital; mortality by day 28 of life; mortality by 12 months of corrected age; duration of antibiotic therapy; duration of hospital stay; moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness); death or moderate or severe neurodevelopmental impairment at or after 12 months of age.

As guideline authors, we are of the viewpoint that all the above-mentioned important outcomes of this guideline are valued highly by all the stakeholders including patients, families, clinicians, policymakers, and the legal system. Therefore, we do not consider that there is any important uncertainty about the importance of these outcomes.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: varies

The microbiological blood culture remains the standard for the diagnosis of LONS. However, in settings where an option of performing blood culture is not available and a serum CRP or PCT level can be evaluated is a viable alternative. However, the limitations of the false positive and false negative tests should always be kept in mind.

Resources required (*How large are the resources required?)*

Judgement: moderate costs

No studies are available that compared the cost of different approaches (CRP versus PCT versus blood culture) for the screening of LONS. The cost incurred in the purchase of the CRP test kit is likely to be lower, and that of PCT is likely to be higher. Qualitative CRP can be performed as a point of care test. Pathology technicians would be required to perform quantitative CRP and PCT tests.

The cost incurred in purchasing automated blood culture systems is likely to be higher. A microbiologist/ pathologist lead microbiological culture also has a human resource cost associated with training and salary.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: no included studies

No studies are available regarding certainty of required resources.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: no included studies

No studies are available regarding certainty of required resources.

Equity (what would be the impact on health equity?)

Judgement: probably increased

Although no studies are available, the availability of a serum CRP test and PCT test is likely to improve the screening of LONS in SNCU settings.

It is expected that most tertiary care settings will have a microbiological laboratory that conducts blood culture through traditional or automated techniques.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: probably yes

There is no evidence against the acceptability of serum CRP and PCT-based screening for the diagnosis of LONS. CRP is the most widely used diagnostic screening test in India and worldwide. In a few tertiary care NICU settings, the PCT test is also used.

CRP screening tests are widely available and relatively inexpensive. Whereas PCT tests are not easily available and likely to be prohibitively expensive in most settings. Therefore, CRP test is likely to be more acceptable than PCT to most stakeholders.

Feasibility (is the intervention feasible to implement?)

Judgement: probably yes

Although no studies are available, CRP and PCT screening in diagnosis of LONS can be made available without major difficulties where blood culture cannot be performed.

RECOMMENDATION

2. The guidelines group suggests that there is NO advantage in using PCT over CRP as a screening test for LONS. Based on currently available best evidence, neither of the index tests (CRP and PCT) are optimal as a screening test for LONS.

Weak recommendation, Moderate certainty of evidence

Justification

Overall justification

Because of the limited accuracy of serum CRP and PCT over blood culture in the diagnosis of LONS, the guideline panel suggests against the routine use of CRP and PCT in the screening of LONS. However, in settings where the reference standard blood culture test is not available, serum CRP may be used as a screening tool as it has modest accuracy.

Detailed justification

Test accuracy

Evaluating a serum CRP level at the assessment of an infant with a 40% pre-test probability of LONS generates a post-test probability of 18% for the negative test result and 80% for a positive test result. Evaluating a serum PCT level at the assessment of an infant with a 40% pre-test probability of LONS generates a post-test probability of 21% for the negative test result and 78% for a positive test result. Therefore, it can be interpreted that determining the CRP or PCT level at the time of initial evaluation of LONS is unlikely to aid in early diagnosis of LONS or to select infants to undergo further investigations or treatment with antimicrobial or other supportive therapy.

Subgroup considerations

Additional data is required on the utility of combinations of CRP ± hematological parameters and PCT over blood culture from low and low-middle income countries like India.

Implementation considerations

Efforts need to be made by health policymakers to make the reference standard blood culture test available in all settings wherever a newborn infant with LONS is assessed and treated. In

places where blood culture test cannot be made available, at least a facility for performing point of care CRP screen in a low-risk population should be made available.

Monitoring and evaluation

Wherever a newborn infant with clinically suspected LONS is tested by using a serum CRP screening test instead of blood culture close clinical monitoring for potential complications and early referral to a higher centre is warranted.

Research priorities

There is an urgent need to investigate for a biomarker that is valid, accurate (accurately predicts presence or absence of infection), reliable (reproducible), simple to perform, one which gives results rapidly, easily available, and economical for early diagnosis of LONS in newborn infants as an alternative to the traditional reference standard blood culture.

***Practice Question 3*: Among newborn infants with probable sepsis (symptomatic EONS or LONS), do CSF rapid diagnostic tests (abnormal CSF cytology/ biochemistry individually & combinations) have a high diagnostic accuracy for diagnosing meningitis (defined by CSF culture/ Gram stain/ PCR)?**

Pico question

P= Neonates with probable sepsis ; I= CSF RDTs (WBC count, glucose, and protein)

C= CSF culture alone; O= Survival until discharge from hospital; Survival until day 28 of life; Survival until 12 months of corrected age; Relapse with culture-positive sepsis; Moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness); Death or moderate or severe neurodevelopmental impairment (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness) at or after 12 months of age; Seizures needing more than one anticonvulsant during follow-up (epilepsy); and Necrotising enterocolitis (stage II or more)

Summary of evidence

Tables 3 A,B and C depict the summary of evidence.

Table 3: Summary of findings table Table 3-A CSF WBC count

Cut-off value: variable ;**Reference test:** CSF gram-stain or culture or PCR

Pooled sensitivity: 0.90 (95% CI: 0.88 to 0.92) | **Pooled specificity:** 0.87 (95% CI: 0.82 to 0.91)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 5% Typically seen in	Prevalence 10% Typically seen in	Prevalence 15% Typically seen in		
True positives	45 (44 - 46)	90 (88 - 92)	135 (132 - 138)	740 (15)	⊕⊕⊕◯ Moderate[a,b,c]
False negatives	5 (4 - 6)	10 (8 - 12)	15 (12 - 18)		
True negatives	827 (779- 864)	783 (738 - 819)	739 (697- 774)	30955 (15)	⊕⊕⊕◯ Moderate[b,c]
False positives	123 (86 - 171)	117 (81 - 162)	111 (76- 153)		

CI: confidence interval

Explanations

a. QUADAS-2 tool was used for assessing the quality of included studies. Of the included 15 studies, 6 studies were adjudged to have high risk of bias in patient selection, 5 studies for index test and 4 studies for flow and timing. All the studies were at low risk of bias for reference standard. When applicability concerns were assessed, 4 studies were adjudged to have a high-risk in patient selection and 1 in reference standard. None of the studies had applicability concerns related to the index test. b. I2 >75% c. Narrow confidence intervals and large sample size

Table 3-B CSF glucose
Cut-off value: variable
Reference test: CSF gram-stain or culture or PCR
Pooled sensitivity:0.71 (95% CI: 0.54 to 0.85) | **Pooled specificity**:0.91 (95% CI: 0.76 to 0.99)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 5% Typically seen in	**Prevalence 10%** Typically seen in	**Prevalence 15%** Typically seen in		
True positives	**36** (27 - 43)	**71** (54 - 85)	**107** (81 - 128)	38 (4)	⊕⊕◯◯ **Low**[a,b,c]
False negatives	**14** (7 - 23)	**29** (15 - 46)	**43** (22 - 69)		
True negatives	**864** (722 - 941)	**819** (684 - 891)	**774** (646 - 842)	1082 (4)	⊕⊕◯◯ **Low**[b,c]
False positives	**86** (9 - 228)	**81** (9 - 216)	**76** (8 - 204)		

CI: confidence interval
Explanations
a. QUADAS-2 tool was used for quality assessment. Of the 4 studies included in the meta-analysis, 2 studies were adjudged as having high risk of bias in patient selection, while 1 study each were adjudged high risk of bias in application of index test and flow and timing. None of the studies had applicability concerns in patient selection.
b.I2 > 75%
c. Wide confidence interval

Table 3-C CSF protein
Cut-off value: variable
Reference test: CSF gram-stain or culture or PCR
Pooled sensitivity:0.92 (95% CI: 0.89 to 0.94) | **Pooled specificity**:0.89 (95% CI: 0.81 to 0.94)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 5% Typically seen in	**Prevalence 10%** Typically seen in	**Prevalence 15%** Typically seen in		
True positives	**46** (45 - 47)	**92** (89 - 94)	**138** (134 - 141)	506 (14)	⊕⊕⊕◯ **Moderate**[a,b]
False negatives	**4** (3 - 5)	**8** (6 - 11)	**12** (9 - 16)		
True negatives	**845** (770 - 893)	**801** (729 - 846)	**757** (689 - 799)	12.692 (14)	⊕⊕⊕◯ **Moderate**[b]
False positives	**105** (57 - 180)	**99** (54 - 171)	**93** (51 - 161)		

CI: confidence interval
Explanations
a. QUADAS-2 tool was used for quality assessment of studies. Of the 14 studies, 8 were adjudged low risk of bias for patient selection, and flow and timing. 9 had low risk of bias for index test and 12 for reference standards used. When applicability concerns were assessed, none had concerns with index test, while 12 were at low risk for patient selection, and 10 were a low risk for reference standard.
b. I2 > 75%

Summary of judgements

Problem (is the problem a priority?):
Judgement: Yes

Bacterial meningitis is an important cause of mortality and morbidity among neonates. Its incidence ranges from 0.21 to 0.5 per 1000 live births in developed countries and 0·8 to 6.1 per 1000 live births in developing countries (13, 45-47). Mortality from neonatal meningitis has decreased significantly in the past three decades. The morbidity, however, continues to be high, with 19-26% having moderate to severe disability and 5-19% having a severe disability on

follow-up (48) . Neonatal meningitis is difficult to diagnose clinically because of non-specific signs that overlap with uncomplicated sepsis.

The laboratory diagnosis of neonatal bacterial meningitis is challenging. In clinical practice, false-negative CSF cultures are common- attributable to delayed processing, prior administration of antibiotics, and low sample volumes. It takes at least 24-48 hours for the CSF culture to be reported positive. Because of the difficulties associated with the reference standard tests, and the ease of performing the above RDTs, the latter is often used to diagnose neonatal meningitis. A wide range of values of sensitivity, specificity, and likelihood ratios have been reported.

Test accuracy (How accurate is the test?):

Judgement: Accurate

The CSF WBC count has a good sensitivity of 0.9 (95% CI: 0.88 to 0.92) and moderate specificity of 0.87 (95% CI: 0.82 to 0.91) based on a meta-analysis of 15 studies (49). CSF glucose estimation has a poor sensitivity of 0.71 (95% CI: 0.54 to 0.85) and good specificity of 0.91 (95% CI: 0.76 to 0.99) based on a meta-analysis of 4 studies. CSF protein has a good sensitivity of 0.92 (95% CI: 0.89 to 0.94) and moderate specificity of 0.89 (95% CI: 0.81 to 0.94) based on a meta-analysis of 14 studies (49).

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: Moderate

The desirable anticipated effects of useful rapid diagnostic tests are the true positive and true negative results. CSF WBC count will correctly identify 45 of 50 neonates with meningitis, when applied on a population of 1,000 neonates with 5% prevalence (or pre-test probability) of meningitis (49). In the same scenario, it will correctly identify 827 of 950 neonates without meningitis. As the pre-test probability increases, the number of false positives decrease further and hence the probability of unnecessary receiving antibiotics for a longer duration. When CSF glucose is applied to the same population, 36 of 50 neonates with meningitis are correctly identified, while 864 out of 950 neonates without meningitis are also correctly identified. CSF protein will identify 46 of 50 neonates with meningitis and 845 of 950 neonates without meningitis.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: Moderate

The undesirable effects are related to probability of under diagnosis and hence, under treatment (False negatives). A lesser concern will be unnecessary prolongation of antibiotic therapy, and related complications, due to over diagnosis. When CSF WBC count is used to diagnose meningitis in a population of 1,000 neonates with suspected meningitis, it will mis-identify 5, 10 and 15 neonates with meningitis as "no meningitis", at 5%, 10% and 20% pre-test probability of meningitis, respectively (49). Similarly, CSF glucose is likely to mis-identify 14, 29 and 43 neonates with meningitis as "no meningitis". The numbers for CSF protein would be 4, 8 and 12 neonates at 5%, 10% and 20% pre-test probability, respectively.

Certainty of evidence of test accuracy (what is the overall certainty of the evidence of test accuracy?):

Judgement: Moderate

For CSF WBC count and protein, there was moderate certainty evidence on sensitivity and specificity. For CSF glucose, there was low certainty evidence for tests sensitivity and moderate certainty evidence for specificity.

Certainty of evidence of test's effects (what is the overall certainty of the evidence for any critical or important direct benefits, adverse effects or burden of the test?):

Judgement: No included studies

None of the studies have evaluated the critical or important direct benefits, adverse effects and burden of the test.

Certainty of evidence of management's effects (what is the overall certainty of the evidence of effects of the management that is guided by the test results?):

Judgement: No included studies

None of the studies have assessed the effects of the management guided by test results.

Certainty of evidence of test result/management (How certain is the link between test results and management decisions?):

Judgement: No included studies

No studies have evaluated the link between test results and management decisions.

Certainty of effects (what is the overall certainty of the evidence of effects of the test?):

Judgement: No included studies

None of the studies have evaluated the certainty of effects.

Values (is there important uncertainty about or variability in how much people value the main outcomes?):

Judgement: No important uncertainty or variability

The diagnostic accuracy of CSF rapid diagnostic tests and downstream effects of survival, relapse, neurodevelopmental impairment, epilepsy, and hydrocephalus were considered important by all panel members.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?):

Judgement: Probably favours the intervention

There were no included studies addressing the balance between desirable and undesirable effects. But, as the 3 CSF rapid diagnostic tests are easy to perform, cost effective with rapid turnaround time, they are likely to influence our decisions on treatment initiation. Given the good diagnostic accuracy of CSF rapid diagnostic tests, the panel of experts arrived at a consensus that the balance of effects is in the favour of using them.

Resources required (How large are the resources required?):

Judgement: Negligible costs and savings

As CSF rapid diagnostic tests of WBC count, glucose and protein are add-on tests, some additional resources may be needed. When a CSF analysis is being done, various resources like personnel, LP sets, needles and culture bottles are needed, even if only the reference standard test were to be performed. For doing CSF rapid diagnostic tests of WBC count, glucose, and protein, we need vacutainers, reagents, machines and personnel for performing lab testing, in addition to the above. These are likely to cause additional cost burden. However, the reagents, machines and personnel are likely to be already available in the health care facility, as these are very basic laboratory investigations.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?):

Judgement: No included studies

None of the studies have assessed the resources required for doing CSF rapid diagnostic tests.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?):

Judgement: No included studies

None of the studies have assessed the cost-effectiveness of doing CSF rapid diagnostic tests.

Equity (what would be the impact on health equity?):

Judgement: Probably increased

CSF rapid diagnostic tests are used to make rapid decisions- regardless of whether culture facilities are available or not. In places where culture, Gram stain and PCR are available, the results of the reference standard tests may override the results of CSF rapid diagnostic tests. However, in a situation where microbiology facilities, especially culture, are not available, CSF rapid diagnostic tests are the only tests that can be performed. In these severely resource restrained settings, CSF rapid diagnostic tests are likely to improve health equity.

Acceptability (is the intervention acceptable to key stakeholders?):

Judgement: Probably yes

As CSF examination is any how required for evaluation of a neonate with sepsis and these rapid diagnostic tests are only add-on tests, whereby they do not alter the decision to do the reference standard (gram-stain or culture or PCR), there are unlikely to be any acceptance issues.

Feasibility (is the intervention feasible to implement?):

Judgement: Yes

The use of CSF rapid diagnostics is feasible in most places, as it needs only a basic pathology and biochemistry services

RECOMMENDATION

3a. The guidelines group suggests using CSF WBC count and protein estimation for diagnosis in neonates being evaluated for suspected meningitis.

Weak recommendation, Moderate certainty of evidence

3b. The group suggests NOT to use CSF glucose estimation for diagnosis in neonates being evaluated for suspected meningitis.

Weak recommendation, Low certainty of evidence

Justification

Overall justification

CSF WBC count and protein are accurate tests in diagnosis of neonatal meningitis. It's even more valuable when there are limitations in microbiological lab services, and when there is antibiotic pre administration.

CSF glucose is not an accurate test in diagnosis of neonatal meningitis. Although an abnormal CSF glucose makes the diagnosis of meningitis likely, a normal CSF glucose doesn't help to rule out a diagnosis of meningitis.

Detailed justification

Problem

Bacterial meningitis is an important cause of mortality and morbidity among neonates. Its incidence ranges from 0.21 to 0.5 per 1000 live births in developed countries and 0·8 to 6.1 per 1000 live births in developing countries. Mortality from neonatal meningitis has decreased significantly in the past three decades. The morbidity, however, continues to be high, with 19-26% having moderate to severe disability and 5-19% having a severe disability on follow-up. Neonatal meningitis is difficult to diagnose clinically because of non-specific signs that overlap with uncomplicated sepsis. The laboratory diagnosis of neonatal bacterial meningitis is challenging. In clinical practice, false-negative CSF cultures are common- attributable to delayed processing, prior administration of antibiotics, and low sample volumes. It takes at least 24-48 hours for the CSF culture to be reported positive. Because of the difficulties associated with the reference standard tests, and the ease of performing the above RDTs, the latter is often used to diagnose neonatal meningitis. A wide range of values of sensitivity, specificity, and likelihood ratios have been reported.

Test accuracy

The CSF WBC count has a good sensitivity of 0.9 (95% CI: 0.88 to 0.92) and moderate specificity of 0.87 (95% CI: 0.82 to 0.91) based on a meta-analysis of 15 studies. CSF glucose estimation has a poor sensitivity of 0.71 (95% CI: 0.54 to 0.85) and good specificity of 0.91 (95% CI: 0.76 to 0.99) based on a meta-analysis of 4 studies. CSF protein has a good sensitivity of 0.92 (95% CI: 0.89 to 0.94) and moderate specificity of 0.89 (95% CI: 0.81 to 0.94) based on a meta-analysis of 14 studies.

Certainty of the evidence of test accuracy

For CSF WBC count and protein, there was moderate certainty evidence on sensitivity and specificity. For CSF glucose, there was low certainty evidence for tests sensitivity and moderate certainty evidence for specificity.

Equity

CSF rapid diagnostic tests are used to make rapid decisions- regardless of whether culture facilities are available or not. In places where culture, Gram stain and PCR are available, the results of the reference standard tests may override the results of CSF rapid diagnostic tests. However, in a situation where microbiology facilities, especially culture, are not available, CSF rapid diagnostic tests are the only tests that can be performed. In these severely resource restrained settings, CSF rapid diagnostic tests are likely to improve health equity.

Acceptability

As CSF examination is anyhow required for evaluation of a neonate with sepsis and these rapid diagnostic tests are only add-on tests, whereby they do not alter the decision to do the reference standard (gram-stain or culture or PCR), there are unlikely to be any acceptance issues.

Subgroup considerations:

None

Implementation considerations:

CSF rapid diagnostic tests are never done separately- they are part of CSF analysis for culture, Gram stain, other rapid tests etc. so trained manpower, LP set, needles and culture tubes/bottles are not required separately for LP. Only extra consideration is the hematology and biochemistry laboratories which analyse CSF WBC, glucose, and protein, and which are widely available.

Monitoring and evaluation:

Lumbar Puncture performed to collect samples for CSF analysis is reasonably safe but there are certain adverse effects that one must look out for. In neonates with hemodynamic instability, bleeding diathesis and local skin and soft tissue infection, LP is contraindicated.

Research priorities:

Observational and randomized control trials are needed to assess the important down-stream effects of using CSF rapid diagnostic tests including mortality and other major morbidities, and cost of care. Also, more studies are needed evaluating accuracy of combinations of tests.

***Practice Question 4*: Among ASYMPTOMATIC newborn infants delivered to mothers with one or more risk factors of EONS, do clinical sepsis scores (comprising maternal & infant risk factors) have a high diagnostic accuracy in diagnosing EONS (defined by culture or PCR)?**

Pico question

P= Asymptomatic neonates delivered to mothers with risk factor(s) for EONS
I= Clinical sepsis scores (containing maternal and infant risk scores)
C= No clinical sepsis score
O= Survival until discharge from hospital; Survival until day 28 of life; Survival until 12 months of corrected age; Relapse with culture-positive sepsis; Moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness); Death or moderate or severe neurodevelopmental impairment (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness) at or after 12 months of age; Seizures needing more than one anticonvulsant during follow-up (epilepsy); and Necrotising enterocolitis (stage II or more)

Table 4: Summary of findings

Pooled sensitivity: 0.49 (95% CI: 0.27 to 0.72) | **Pooled specificity**: 0.87 (95% CI: 0.77 to 0.93)

Test result	Number of results per 1,000 patients tested (95% CI)			Number of participants (studies)	Certainty of the Evidence (GRADE)
	Prevalence 0.5% Typically seen in	**Prevalence 2%** Typically seen in	**Prevalence 5%** Typically seen in		
True positives	**2** (1 to 4)	**10** (5 to 14)	**25** (14 to 36)	11 (10)	⨁⨁◯◯ **LOW** a,b,c,d
False negatives	**3** (1 to 4)	**10** (6 to 15)	**25** (14 to 36)		
True negatives	**866** (766 to 925)	**853** (755 to 911)	**827** (731 to 884)	3170 (10)	⨁⨁◯◯ **LOW** a,d,e
False positives	**129** (70 to 229)	**127** (69 to 225)	**123** (66 to 219)		

CI: Confidence interval

Explanations

a. Of the 10 studies included in meta-analysis, none of the studies had risk of bias in patient selection, use of index test and reference standard. 6 studies had risk of bias in flow and timing, because all the subjects did not receive the reference standard. When applicability concerns were assessed, 6 studies had concerns in patient selection, 3 studies had concerns in index test and none in reference standard.

b. The inconsistency, as measured by I^2 statistic is low (36.28)

c. The pooled sensitivity has a very wide confidence interval. The sensitivities ranged from 0 to 100%

d. The Deeks funnel plot shows asymmetry in the distribution of diagnostic odds ratios. The bias coefficient was 15.24 (1.9, 28.57) and p value was 0.03

e. The inconsistency, as measured by I^2 statistic is high (97.3)

Summary of judgements

Problem (is the problem a priority?)

Judgement: Yes

EONS is a rare but significant cause of mortality and morbidity in neonates. Current guidelines/practice led to large numbers of well babies receiving antibiotics. The use of a calculator as part of a strategy of managing neonatal EONS adds an objective element to the decision-making algorithm for antibiotic administration. Appropriate use of EONS calculator can decrease use of antibiotics in asymptomatic neonates born with risk factors for early onset sepsis.

Test accuracy (How accurate is the test?)

Judgement: Inaccurate

Meta-Analysis of 10 observational studies (50-59) The EONS calculator has poor sensitivity, but good specificity in diagnosis of early onset sepsis. That means, an abnormal result on EONS calculator (positive test) may miss cases of EONS, but a normal result on EONS calculator (negative test) makes the diagnosis of EONS unlikely.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: Large

The desirable anticipated effects of useful rapid diagnostic tests are the true positive and true negative results. The EONS calculator (Kaiser Permanente) will correctly identify 2 of 5 neonates with early onset sepsis (culture proven), when applied on a population of 1,000 neonates with 0.5% prevalence (or pre-test probability) of early onset sepsis. In the same scenario, it will correctly identify 866 of 995 neonates without early onset sepsis. As the pre-test probability increases, the number of false positives does not decrease further.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: Trivial

The undesirable effects are related to probability of under diagnosis and hence, under treatment (False negatives). A lesser concern will be unnecessary prolongation of antibiotic therapy, and related complications. When EONS calculator is used to diagnose early onset sepsis in a population of 1,000 neonates with suspected meningitis, it will misidentify 3, 10 and 25 neonates with EONS as "no EONS", at 0.5%, 2% and 5% pre-test probability of meningitis, respectively.

Certainty of evidence of test accuracy (what is the overall certainty of the evidence of test accuracy?)

Judgement: Low

There is low certainty of evidence on test sensitivity and specificity. There were only 11 cases of EONS across the 10 studies included in meta-analysis, hence the estimates are likely to be inaccurate. More data is needed to arrive at an accurate estimate of sensitivity.

Certainty of the evidence of the test's effects (What is the overall certainty of the evidence for any critical or important direct benefits, adverse effects, or burden of the test?)

Judgement: Low

There is moderate certainty evidence from single observational studies that use of EONS calculator in asymptomatic newborns exposed to maternal chorioamnionitis does not change the rates of survival before hospital discharge (OR: 6.39; 95% CI: 0.24 - 169.24) (60) and relapse with culture positive sepsis or meningitis (OR: 0.49; 95% CI: 0.02 - 12.20) (56). There was no data available for other critical outcomes of 1. Survival until day 28 of life; 2. Survival until 12 months of corrected age; 3. Moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness); 4. Death or moderate or severe neurodevelopmental impairment (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness) at or after 12 months of age; 5. Seizures needing more than one anticonvulsant during follow-up (epilepsy); 6. Necrotising enterocolitis (stage II or more); and 7. Chronic renal failure

There is high quality evidence from a single observational study (54) that use of EONS calculator in asymptomatic newborns exposed to maternal chorioamnionitis decreases duration of hospital stay (M.D: -1.6 days; 95% CI: -0.56 to -2.64) . There is high certainty evidence from 5 observational studies (54, 56-59) for decrease in antibiotic usage rates (OR: 0.12; 95% CI: 0.10 - 0.15). There is moderate certainty evidence from a single study (54) that the EONS calculator does not change cost of care significantly (MD: -$3,100; 95% CI: $1018.45 to -$7218.45). There was no data available for other important outcomes of 1. Relapse with culture negative (probable) sepsis or meningitis or urinary tract infection; 2. Days to reach full enteral feeds; and 3. Serious adverse drug reactions.

There was high certainty evidence from 3 studies (54, 57, 59) for decreased need for sending blood cultures (OR: 0.10; 95% CI: 0.07 - 0.15) and high certainty evidence from 2 studies (54, 56)

for decreased need for NICU admission (OR: 0.05; 95% CI: 0.03 - 0.08). One study (59) has shown a decrease in the median number of antibiotic doses administered for asymptomatic neonates with risk factors for EONS [8 (IQR: 5 - 14) vs 4 (IQR: 4 - 8) doses].

Certainty of the evidence of management's effects (What is the overall certainty of the evidence of effects of the management that is guided by the test results?)

Judgement: Low

Few prospective observational studies have shown that management of asymptomatic neonates with risk factors for early onset sepsis, based on EONS calculator, can result in significant decrease in resources utilised (sepsis screen, blood cultures, antibiotics, NICU admissions and duration of hospital stay).

Certainty of the evidence of test result/management (How certain is the link between test results and management decisions?)

Judgement: Low

Few studies have assessed the agreement between EONS calculator results and management decisions taken. While there was some difficulty to begin with, most of them have been overcome after sustained efforts, which included quality improvement initiatives and training of personnel.

Certainty of effects (What is the overall certainty of the evidence of effects of the test?)

Judgement: Low

There is low quality evidence from observational studies on critical outcomes of survival before hospital discharge and need for readmissions with culture positive sepsis. The evidence is likely to change with further studies. Moreover, for several other critical outcomes, no data was available.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: No important uncertainty or variability

The "diagnostic accuracy of clinical sepsis scores" and the downstream consequences of using EONS calculator on important neonatal outcomes as mentioned, were considered important by all panel members.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: Probably favours the intervention

EONS calculator use can decrease antibiotic use and cost of care in neonates, but in rare occasions can miss cases of EONS.

Resources required (How large are the resources required?)

Judgement: Negligible costs and savings

Implementation of EONS calculator needs some changes in the unit's database, which can be done with help of IT professionals. However, the potential savings resulting from decreased use of investigations, antibiotics, and shortened NICU and hospital stay are likely to result in large cost savings. However, there is no evidence to support the same.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: Moderate

Only 1 study (54) evaluated the cost savings incurred by using the EONS calculator. They did not note a significant decrease in cost of care (MD: -$3,100; 95% CI: $1018.45 to -$7218.45).

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: Does not favour either the intervention or the comparison

The cost-savings incurred are likely to be more than the cost of implementing EONS calculator. However, available evidence does not show any cost savings.

Equity (what would be the impact on health equity?)

Judgement: Probably reduced

The EONS calculator is based on investigations, which may not be performed in all set-ups. Also, in units handling outborn neonates, the data may be unreliable or unavailable, making it difficult to use.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: No

The EONS calculator which was used in all the published studies was designed and validated in developed countries, where maternal GBS colonization is an important risk factor for EONS. The same calculator cannot be used in the Indian population, and hence there are important concerns. Also, the sensitivity is very poor (about 50%) and the likelihood of missing a case of EONS can affect the acceptability of this diagnostic testing. The downstream consequences, where there was no difference in some of the critical outcomes, are also not favouring use of EONS calculator.

Feasibility (is the intervention feasible to implement?)

Judgement: Yes

The intervention is feasible to implement, as was shown in several studies. Quality improvement initiatives have helped in increasing the use of EONS calculator.

RECOMMENDATION

4. The guidelines group suggests NOT using the various early-onset sepsis calculators (e.g., the EONS calculator by Kaiser Permanente network) developed in high-income countries for the management of well-appearing, asymptomatic neonates born at or after 35 weeks with risk factors for early onset sepsis.

Weak recommendation, Low certainty of evidence

In select units where predominantly in-born neonates are treated and maternal Group B Streptococcus colonization is an important risk factor for EONS, this calculator can be considered.

Justification

Overall justification

There is very low-quality evidence favouring use of clinical sepsis scores in well-appearing neonates at risk of early onset sepsis (EONS)

Detailed justification

Problem

EONS, although very uncommon in neonates >34 weeks, can have serious morbidity and mortality, if undiagnosed. There is significant over treatment and over investigation of neonates for EONS

Test accuracy

The EONS calculator has poor sensitivity, but excellent specificity.

Desirable Effects

The EONS calculator had high specificity and as a result a lesser number of neonates received antibiotics without any harm noted in critical outcomes.

Undesirable Effects

EONS calculator misses about 50% neonates with culture proven EONS.

Certainty of the evidence of test accuracy

There is low certainty evidence on test accuracy (sensitivity and specificity).

Certainty of the evidence of test's effects

There is low certainty evidence indicating that there is no change in the critical outcomes of mortality and readmissions with sepsis.

Values

All the panel members considered the use of Clinical Sepsis Scores as an important question.

Cost effectiveness

There is moderate certainty evidence for no change in cost of care.

Equity

Equity is probably decreased as it cannot be used without necessary investigations and in out born units.

Acceptability

As the scores are derived and validated in developed countries, where maternal GBS is an important risk factor for EONS, they are unlikely to be accepted by doctors and administrators working in India

Feasibility

Use of EONS calculator is feasible as shown in several studies.

Subgroup considerations

More data is needed on neonates born in developing countries, late preterm neonates and neonates with growth restriction. Studies need to be conducted in developing countries, primary care centres and settings with limited resources, both for generation of clinical sepsis scores and validation of this data.

Implementation considerations

As shown in observational and quality improvement studies, efforts are needed to introduce and successfully implement the sepsis calculators in neonatal units.

Monitoring and evaluation

Close monitoring of the data and periodic evaluation of test accuracy and neonatal outcomes must be done in units using clinical sepsis scores, till high quality evidence is available.

Research priorities

Further studies are needed to develop context specific clinical sepsis calculators and validate them in prospective studies. Observational or randomized trials are also needed to evaluate the downstream consequences of using such calculators.

Practice Question 5: **Among asymptomatic newborn infants with maternal-infant risk factors of EONS is administration of antibiotics if symptoms develop non-inferior to administration of antibiotics from birth?**

Pico question

P= Asymptomatic newborn infants with maternal-infant risk factors for EONS
I= Antibiotics administered if symptoms develop
C= Antibiotics administered immediately at birth
O= mortality during hospital stay, mortality within day 28 of life, mortality by 12 months of corrected age(survival until 12 months of corrected age), duration of antibiotic therapy, duration of hospital stay, antibiotic usage rates(proportion of neonates on antibiotics), serious adverse drug reactions and cost of care.

Summary of evidence

Tables 5 depicts the summary of evidence.

Table 5: Summary of findings

Patient or population: asymptomatic newborn infants with maternal-infant risk factors for early onset neonatal sepsis
Setting: neonates born with maternal-infants risk factors for Early onset neonatal sepsis
Intervention: antibiotics if symptoms develop
Comparison: antibiotics administered immediately from birth

	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments/Outcomes
	Risk with antibiotics administered immediately from birth	**Risk with antibiotics if symptoms develop**				
Mortality during hospital stay	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 3.82** (0.15 to 95.93)	224 (3 observational studies)	⨁⨁◯◯ Low a,b	Mortality during hospital stay was not different in neonates with maternal-infant risk of EONS ,in those receiving antibiotics at birth in comparison to if symptoms developed.
Mortality within day 28 of life	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	116 (2 RCTs)	⨁⨁◯◯ Low c	Given outcome not reported by any study
Mortality by 12 months of corrected age (Survival until 12 months of corrected age)	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	Given outcome not reported by any study
Duration of antibiotic therapy	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	Given outcome not reported by any study
Duration of hospital stay		MD **1 days fewer** (1.09 fewer to 0.91 fewer)	-	1000 (1 observational study)	⨁⨁◯◯ LOW ᵅ	The duration of hospital stay was found to be lower by mean duration of 1 day (95% CI as 1.09 days fewer to 0.91 days fewer)in neonates with maternal-infant risk factors of EONS, who received antibiotics if symptoms develop as compared to those with antibiotic

						administration immediately after birth.
Antibiotic usage rates (proportion of neonates on antibiotics)	123 per 1,000	**47 per 1,000** (40 to 54)	**RR 0.38** (0.33 to 0.44)	9975 (4 observational studies)	⊕⊕⊕⊕ High d	Reduction in antibiotic usage rates to 47/1000 (95% CI 40-54 per 1000), 62% reduction ;if antibiotics are administered only if symptoms occur as compared to antibiotics initiated at birth in neonates with maternal-infant risk factors of EONS.
Serious adverse drug reactions	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	Given outcome not reported by any study
Cost of care	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	Given outcome not reported by any study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations
a. The studies included are 2 poor quality RCTs and 1 observational study. Both RCT's have no proper randomisation method. For observational study- In confounding domains: Baseline variables such as- perinatal asphyxia, MSAF not matched amongst both groups, Time varying variables such as maternal GBS screening and IAP different in 2 groups. Co-interventions such as NICU practices, delivery room practices, hand hygiene rates, Breastfeeding rates, type of EONS organisms and their profile not measured; risk of bias for baseline confounding variables- serious; risk of bias due to deviation from intended intervention is serious as 25% neonates in intervention group underwent lab test and received antibiotics when cultures were available
b. Very few events of interest in intervention group and none in control group, hence generating very wide confidence intervals leading to imprecision
c. Very few numbers of participants with none of them having outcome of interest in any group, Lack of proper randomization,
d. The studies included are 2 poor quality RCTs and 2 observational studies. Both RCT's have no proper randomization method. One of the observational studies has ROBINS i-tool as serious bias as mentioned in explanation a, while other has critical bias in confounding domain due to lack of baseline variables matching- Gestation, birth weight along-with all other criteria mentioned previously in b. So rated as serious.

Summary of judgements

Problem (is the problem a priority?)

Judgement: Yes

Neonatal sepsis is the second most common cause of neonatal mortality after prematurity in our country. As per the last NNPD report, the incidence recorded is 30/1000 live births in hospital-based studies and 2.7-17% from the community setting (61). However, a recent large hospital-based cohort study found an incidence of 14.3% with 75% of all sepsis episodes occurring within the first 72hrs of life (5). Despite such a significant bearing on NMR, huge variability exists in defining neonatal sepsis and its causative risk factors. Also, associations between maternal-neonatal risk factors and EONS is not strongly established (62). To add to

this several sets of international and national guidelines exist for the management of these at-risk neonates which contributes to wide heterogeneity in their treatment practices (63).Empiric antibiotic treatment for all at-risk neonates from birth has been recommended by the majority of international guidelines. However, such a policy exposes a significant number of neonates to both short and long-term adverse effects of unnecessary antibiotic administration and overburdening the system with such admissions (64).Many recently conducted studies have proven the benefit of serial clinical examination of these neonates as a better management option (65) .This approach is now being recommended by international societies for the management of well-appearing neonates with potential risk factors for EONS (66). Evidence for the same from the developing world is scarce. The high crude birth rate, high sepsis-related neonatal mortality rate and huge variability in managing these neonates makes it a priority problem in our setting (67).

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: Varies

One of the important outcomes- Antibiotic usage rates - was assessed in 2 poor quality RCTs and 2 observational studies. The pooled effect was a significant relative decrease of risk by 62%, with RR of 0.38 (95% CI 0.33-0.44). The quality of evidence was high owing to the absence of inconsistency, indirectness, and imprecision were not noted. Reduction in antibiotic usage has an important bearing on the health care system by reducing unnecessary antibiotic exposure and hospital stay. Other outcomes that were deemed as important such as duration of hospital stay, duration of antibiotic therapy and cost of care have not been reported by any studies in literature.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: Don't Know

If antibiotics are administered after an at-risk neonate develops symptoms as compared to empiric treatment starting at birth, there is a potential risk of missing some neonates that have septicaemia. Delayed detection or inadequate treatment may lead to adverse outcomes, including death. Therefore, mortality during the hospital stay, at day 28 of life, and by 12 months of corrected age were chosen as the critical undesirable outcomes. Neither of the two RCTs reported mortality as an outcome (68) and a single observational study reported one death in the intervention group during hospital stay (64). Hence combining the evidence showed no significant increase in mortality caused due to the intervention with anticipated absolute effect of 0 per 1000 live births (95% CI 0-0). Quality of evidence was graded as low due to serious risk of bias and very serious imprecision

Certainty of evidence (what is the overall certainty of the evidence of effects?)

Judgement: Low

For all the critical and important outcomes assessed, only 2 poor quality randomized controlled trials and 2 observational studies with either serious or very serious risk of bias are available for inclusion in the systematic review. Furthermore, the event rate was observed to be low for critical outcomes. Therefore, the risk estimates are imprecise with 95%CI around the pooled estimate including both 1) no effect and 2) appreciable benefit or appreciable harm. The actual risk estimate may likely be substantially different from the one pooled from existing literature. The only important outcome that seems to have been significantly affected is the reduction in antibiotic usage rates that has moderate quality of evidence.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: No important uncertainty or variability

The guidelines panel is of viewpoint that mortality during hospital stay, during the neonatal period and at 12 months of corrected age, are the appropriate critical outcome of this guideline as are valued highly by all the stakeholders including patients, families, clinicians, and policymakers. Therefore, we do not consider that there is any important uncertainty about the importance of this outcome. Other outcomes like antibiotic usage rates, duration of hospital stay etc. may be rated differently by patients, families, clinicians, or policymakers; however, we believe that these are not as critical as mortality.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: Probably favours intervention

Detailed judgements for this criterion include the judgements regarding each of the four preceding criteria:

· Is there important uncertainty about or variability in how much people value the main outcomes? No important uncertainty or variability

· What is the overall certainty of the evidence of effects? Low

· How substantial are the desirable anticipated effects? Varies. The only beneficial effect noted was a reduction in antibiotic usage rates.

· How substantial are the undesirable anticipated effects? Don't know. Sufficient data comparing critical outcomes i.e., mortality doesn't exist, and adverse drug reactions are not documented by any of the studies.

In view of inadequate evidence of the intervention on effect of mortality; recommendations for use of this intervention (antibiotic administration if a neonate is born with risk factors for sepsis develops symptoms) are probably yes for neonates born at ≥ 35 weeks of gestation and probably no for neonates born at < 35 weeks of gestation.

Resources required (*How large are the resources required?)*

Judgement: Moderate savings

Reducing the antibiotic exposure, improving antibiotic stewardship, decreasing the need for sending investigations in asymptomatic neonates and reducing hospitalisation rate and duration of at-risk well-neonates. These all seem to have a positive impact on reducing health care burden and unnecessary expenditure. Investments need to be done in terms of recruitment of an adequate number of healthcare professionals especially nurses and physicians along with their training for vigilant serial monitoring and timely identification of signs and symptoms of evolving sepsis. Though building human resources is a beneficial investment as it can create subsequent health care protocols and internal training, teaching and feedback can be made a part of their routine clinical care practices.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: No included studies

No evidence is available regarding the certainty of evidence of the required resources. The cost of serial examination depends not only on availability of human resources and their training (which may be fixed), but also on other adjunct costs which are variable and need to be studied - such as keeping apparently well babies with risk factors for in- hospital monitoring for 48-72 hours and creation of extra ward/ beds in units for monitoring these neonates once

a mother is discharged, along with feasibility of sustaining standardised monitoring protocols in presence of rapidly changing staff in secondary and tertiary care health facilities.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: No included studies

The cost-effectiveness of the treatment approach has not been investigated in any randomized controlled trial or observational study.

Equity (what would be the impact on health equity?)

Judgement: Probably increased

In view of inadequate evidence of the intervention on effect of mortality; recommendations for use of this intervention (antibiotic administration if a neonate is born with risk factors for sepsis develops symptoms) are probably yes for neonates born at ≥ 35 weeks of gestation and probably no for neonates born at < 35 weeks of gestation. In view of non-exposure to empiric antibiotics to higher gestational age group and management of neonates with serial observations, the equity of health care might increase as no drugs need to be purchased by parents/ caretakers at birth for asymptomatic at-risk neonates, and rooming-in can be done at birth for all the neonates so avoiding bed charges for neonates.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: Probably Yes

In view of inadequate evidence of the intervention on effect of mortality; recommendations for use of this intervention (antibiotic administration if a neonate is born with risk factors for sepsis develops symptoms) are probably yes for neonate born at ≥ 35 weeks of gestation and probably no for neonates born at < 35 weeks of gestation**.** Given avoiding the need for unnecessary intravenous cannulation, investigations, and promoting rationale antibiotic administration and rooming-in of ≥ 35 weeks gestational age neonates with mothers, the intervention seems acceptable to all stakeholders. For <35 weeks gestational age recommendations are probably No for following the intervention and treatment to be done as previously with empiric antibiotics for at risk neonates till sepsis is ruled out.

Feasibility (is the intervention feasible to implement?)

Judgement: Probably Yes

The intervention is feasible to implement considering the advantages offered to all stakeholders.

RECOMMENDATION

5a. The guidelines group suggests administering antibiotics in *symptomatic*[+] neonates born at any gestation *and* having maternal-perinatal risk factors[¶] of early-onset sepsis.

Weak recommendation, Low certainty of evidence

5b. The guidelines group suggests considering initiation of antibiotic therapy in asymptomatic preterm neonates born before 35 weeks of gestation *and* having maternal-perinatal risk factors[¶] of early-onset sepsis. In the >32 weeks' gestation group, antibiotics may be considered for any one red flag risk factor or ≥2 yellow flag risk factors; and in the ≤32 weeks' gestation group for either one red or one yellow flag risk factor.

Weak recommendation, Not graded (Expert consensus)

5c. In case antibiotics are started, the guidelines group recommends that antibiotics may be stopped after 36 hours if the blood culture remain sterile, the baby's clinical condition remains stable, and there are no signs suggestive of sepsis.

Strong recommendation, Not graded(Expert consensus)

[+] Clinical illness consisting of abnormal vitals such as: Tachycardia (Heart Rate≥ 160/min), Tachypnea (≥60/min), and/or Temperature instability (fever ≥ 100.4 degree C), supplemental oxygen requirement and/or need for continuous positive airway pressure, mechanical ventilation, or blood pressure support can be used as a predictor of early-onset infection. There is no evidence that hypoglycemia alone in an otherwise well-appearing infant is a risk factor for early onset sepsis. A newborn's clinical condition often evolves over initial hours after birth, and hence physician's discretion is advised to distinguish transitional symptoms from signs of clinical sepsis (66).

[¶] **Risk factors of early-onset sepsis** (69)

Red flag risk factors
Clinical diagnosis of Chorioamnionitis Fever – either ≥39.0°C once or 38.0°C to 38.9°C on two or more measurements 30 minutes apart without another clear source PLUS one or more of the following: (a) Baseline fetal heart rate >160 beats/min for ≥10 minutes, excluding accelerations, decelerations, and periods of marked variability, (b) Maternal white cell (WBC) count >15,000/mm^3 in the absence of corticosteroids and ideally showing a left shift, (c) Purulent-appearing fluid coming from the cervical os visualized by speculum examination.
Foul smelling Liquor
Other risk factors (Yellow flag risk factors)
Preterm premature rupture of membranes
Rupture of membranes for ≥ 18 hours
Intrapartum fever ≥ 38°C in presence of suspected or confirmed bacterial infection
Dai handling or unclean vaginal examination /delivery surface/cord tie

Justification

Overall justification

Careful standardized monitoring and clinical examination can be used for neonates ≥35 weeks gestation with maternal-infant risk factors for sepsis.

Detailed justification

Desirable Effects

Reduction in antibiotic usage rates and more rationale usage of antibiotics, decreased hospital stay without any impact on mortality

Undesirable Effects

Possibility of missing potentially septic neonates at early stages hence delaying treatment, causing adverse outcome in form of meningitis, respiratory/ and cardiovascular failure and in worst case scenario causing mortality.

Subgroup considerations

As studies have looked at neonates with ≥35wks gestation, hence guidelines can be applied to this subset and avoiding lower gestational ages as evidence in favour of recommendations at < 35 weeks doesn't exist.

Implementation considerations

Adequate number and training facilities need to be created uniformly across secondary and tertiary setups along with the building of standardized well tested neonatal monitoring protocols.

Monitoring and evaluation

Careful formulation and dissemination of standardized monitoring protocols need to be established along with data recording preferably through a common digital platform of all high-risk neonates being managed with a said recommendation so that evidence can be strengthened and further refined for generalized applicability

Research priorities

Electronic data recording of all neonates being managed with the approach needs to be maintained rigorously and analysed periodically to assess its impact on neonatal mortality rate, duration of hospitalization and other important outcomes. Simultaneous ways of human resource strengthening and long-term outcome of these neonates in terms of readmission rates and survival until infancy needs to be accessed.

***Practice Question 6*: Among asymptomatic infants at risk of EONS, is administration of antibiotics once lab tests are reported positive non-inferior compared to administration of antibiotics from birth?**

Pico question

P= Asymptomatic newborn infants with maternal-infant risk factors for EONS

I= Antibiotics administered if laboratory tests are positive

C= Antibiotics administered immediately at birth

O= mortality during hospital stay, mortality within day 28 of life, mortality by 12 months of corrected age (survival until 12 months of corrected age), duration of antibiotic therapy, duration of hospital stay, antibiotic usage rates (proportion of neonates on antibiotics), serious adverse drug reactions and cost of care.

Summary of evidence

Table 6 shows the summary of evidence.

Table 6: Summary of findings

Patient or population: asymptomatic infants at risk of EONS. Decrease/increase mortality and other complications
Setting: Infants at risk of EONS
Intervention: antibiotics administered once lab tests are positive
Comparison: immediately at birth

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with immediately at birth	**Risk with antibiotics administered once lab tests are positive**				
Mortality during hospital stay	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	234 (1 observational study)	⨁⨁◯◯ Low[a,b,c,d]	
Mortality within 28 days of life - not measured	-	-	-	-	-	
Mortality by 12 months of corrected age - not measured	-	-	-	-	-	
Duration of antibiotic therapy (Doses)	The median duration of antibiotic therapy was **6** doses	MD **6 doses fewer** (8.01 fewer to 3.99 fewer)	-	234 (1 observational study)	⨁◯◯◯ Very low[a,b,d,e]	
Duration of Hospital stay	The median duration of Hospital stay was **2** days	MD **0 days** (0.38 lower to 0.38 higher)	-	234 (1 observational study)	⨁⨁◯◯ Low[a,b,d,f]	
Antibiotic usage	967 per 1,000	**0 per 1,000** (0 to 232)	**RR 0.00** (0.00 to 0.24)	234 (1 observational study)	⨁⨁◯◯ Low[a,b,d,g]	
Serious adverse reaction - not reported	-	-	-	-	-	

Cost of Care Scale from: 0 to 300	The mean cost of Care was **341.59** dollars	MD **300 dollars fewer** (0 to 0)	-	234 (1 observational study)	⊕⊕◯◯ Low[a,b,d,h]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations
a. Serious risk of bias - observational before-after quality improvement study
b. With single eligible study we did not downgrade for inconsistency across the study results
c. Outcome of interest is nil in both groups, RR not estimable.
d. The number of studies = one, too few to evaluate publication bias
e. wide IQR around median
f. Length of stay data given in median IQR (not normally distributed)
g. Antibiotic usage data given in median IQR (not normally distributed)
h. Method of cost reduction was done from an indirect estimate of the cost incurred per patient in various subheadings like investigations, clinical monitoring and consumables rather than the difference of average cost of care incurred per patient. Indirect cost like loss of working hours of parents due to hospital stay have not been reported. or estimated . Mean cost saved per patient if antibiotics were administered once laboratory reports were positive was reported as 300 dollars.

Summary of judgements

Problem (is the problem a priority?)

Judgement: Yes

Neonatal sepsis is the second most common cause of neonatal mortality after prematurity in our country. As per the last NNPD report, the incidence recorded is 30/1000 live births in hospital-based studies and 2.7-17% from the community setting (61). However, a recent large hospital-based cohort study found an incidence of 14.3% with 75% of all sepsis episodes occurring within the first 72hrs of life (5). Despite such a significant bearing on NMR, huge variability exists in defining neonatal sepsis and its causative risk factors. Also, associations between maternal-neonatal risk factors and EONS is not strongly established (70).To add to this several sets of international and national guidelines exist for the management of these at-risk neonates which contributes to wide heterogeneity in their treatment practices (71, 72). Empiric antibiotic treatment for all at-risk neonates from birth has been recommended by the majority of international guidelines (66). However such a policy exposes a significant number of neonates to both short and long-term adverse effects of unnecessary antibiotic administration and overburdening the system with such admissions (73).Many recently conducted studies have proven the benefit of serial clinical examination and laboratory tests based antibiotic administration for these neonates as a better management option (50). This approach is now being recommended by international societies for the management of well-appearing neonates with potential risk factors for EONS (66).Evidence for the same from the developing world is scarce. The high crude birth rate, high sepsis-related neonatal mortality rate and huge variability in managing these neonates makes it a priority problem in our setting.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: Large

Antibiotic usage rates were assessed in this single observational study(74).The effect was a significant decrease in risk of antibiotic exposure by at least 76%, RR 0.24 95% CI (00-0.24),there was no difference in mortality during the hospital stay when the antibiotics were administered based on the laboratory screening strategy. For the duration of antibiotic therapy (doses) there was a mean difference of 6 higher doses in the group where immediate antibiotics were started at birth and in cost of care there was a mean difference of 300$ higher per infant in

the group where antibiotics were started at birth. Median duration of hospital stay was no different between the two groups. The quality of evidence was high, for the nature of outcome blinding was not feasible and outcomes like antibiotic usage and hospital stay have minimal bias measurement. Since only a single study was eligible for analysis, we assumed no serious inconsistency and publication bias in the study results. Indirectness, and imprecision were not noted.

Reduction in antibiotic usage has an important desirable effect with short course of antibiotics at the level of the individual patient like shorter duration of hospitalization and antibiotic therapy; and at the level of the healthcare facility are decrease in the incidence of multidrug-resistant (MDR), extremely drug-resistant (XDR) and pan drug-resistant bacteria (PDR), and decrease in the incidence of fungal sepsis. The panel did not a priori plan to assess the decrease in the incidence of MDR, XDR and PDR bacterial and fungal sepsis in the healthcare facility, as these outcomes can only be compared in a before and after study design, or in large cluster-randomized trials or after short course of antibiotics is implemented in the unit as a policy for all infants. Nevertheless, during the literature search, none of the studies reported on these outcomes.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: Don't Know

If antibiotics are administered after an at-risk neonate who has positive laboratory tests as compared to empiric treatment starting at birth, there is a potential risk of missing some neonates that have septicaemia. Delayed detection or inadequate treatment may lead to adverse outcomes, including death. Therefore, mortality during the hospital stay, at day 28 of life, and by 12 months of corrected age were chosen as the critical undesirable outcomes. The included study did not report mortality as an outcome. A substantial harm in the form of any case of true EONS where treatment is missed based on laboratory testing (which would require re-hospitalization and re-treatment). Delayed detection or inadequate treatment may lead to adverse outcomes like meningitis, ventriculitis and death. In this single eligible study, there was no reported mortality in either cohort and the follow up mortality at 28 day of life and by 12 months was not measured. There were no readmissions within one week of post discharge but relapse of infections and long-term neurodevelopmental outcomes were not measured.

Certainty of evidence (what is the overall certainty of the evidence of effects?)

Judgement: Low

For all the critical and important outcomes assessed, only 1 observational study with no serious risk of bias is available for inclusion in the systematic review. There was no mortality reported in the cohort of neonates who received antibiotics after the laboratory reports were positive. There was significant reduction in the antibiotic usage in this group with low quality of evidence due to the possible bias.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: No important uncertainty or variability

The guidelines panel is of viewpoint that mortality during hospital stay, during the neonatal period and at 12 months of corrected age, are the appropriate critical outcome of this guideline as are valued highly by all the stakeholders including patients, families, clinicians, and policymakers. Therefore, we do not consider that there is any important uncertainty about the importance of this outcome. Other outcomes like antibiotic usage rates, duration of

hospital stay etc. may be rated differently by patients, families, clinicians, or policymakers; however, we believe that these are not as critical as mortality.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: Probably favours intervention

Overall, the moderate quality evidence indicates a possible beneficial effect of antibiotic administration once a neonate has positive lab tests by lowering antibiotic usage rates. This advantage of rational usage of antibiotics while carefully monitoring at-risk neonates with laboratory screening tests needs to be balanced against missed cases of sepsis leading to re-hospitalization and re-treatment and morbidities like meningitis. In the absence of immediate and long term follow up for morbidities and neurodevelopmental outcomes it is difficult to recommend the intervention over the currently widely practiced strategy of immediate administration of antibiotics.

Detailed judgements for this criterion include the judgements regarding each of the four preceding criteria:

Overall, the high quality of evidence indicates a possible beneficial effect of antibiotic administration once a neonate has a positive lab test by lowering antibiotic usage rates. This advantage of rational usage of antibiotics while carefully monitoring at-risk neonates with laboratory screening tests needs to be balanced against missed cases of sepsis leading to re-hospitalization and re-treatment and morbidities like meningitis. In the absence of immediate and long term follow up for morbidities and neurodevelopmental outcomes it is difficult to recommend the intervention over the currently widely practised strategy of immediate administration of antibiotics.

Detailed judgements for this criterion include the judgements regarding each of the four preceding criteria:

· Is there important uncertainty about or variability in how much people value the main outcomes? No important uncertainty or variability

· What is the overall certainty of the evidence of effects? High

· How substantial are the desirable anticipated effects? Varies. The beneficial effects noted were a reduction in antibiotic usage rates and cost of care.

· How substantial are the undesirable anticipated effects? Don't know. No data on post discharge follow up of the infants.

In view of inadequate evidence of the follow up data; recommendations for use of this intervention (antibiotic administration if a neonate is born with risk factors for sepsis develops symptoms) are probably yes for neonates born at ≥ 35 weeks of gestation and probably no for neonates born at < 35 weeks of gestation.

Resources required (*How large are the resources required?)*

Judgement: Moderate savings

Reducing the antibiotic exposure, improving antibiotic stewardship, and reducing hospitalisation rate and duration of stay in at-risk well-neonates when antibiotics are administered only when laboratory tests are positive. These all seem to have a positive impact on reducing health care burden and unnecessary expenditure. Investments need to be done in terms of setting up laboratory infrastructure and recruitment of an adequate number of healthcare professionals like laboratory personnel. Setting up the laboratory infrastructure and cost of tests might involve additional costs.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: No included studies

No evidence is available regarding the certainty of evidence of the required resources. The cost of laboratory tests depends not only on availability and feasibility of standardised testing protocols both in secondary and tertiary care health facilities. Investments need to be done in terms of setting up laboratory infrastructure and recruitment of an adequate number of healthcare professionals like laboratory personnel.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: Probably favors the intervention

Overall, the cost effectiveness favours antibiotic administration once laboratory tests are positive. The cost reduction in terms of need of lab tests, nursing care and monitoring costs incurred, and antibiotic doses and consumables required was decreased significantly by a mean difference of 300$ per infant when antibiotics were started once lab tests were positive. Even though the cost estimation was not direct per patient cost incurred it was estimated indirectly by per unit reduction of various services and consumables, indirect cost like loss of parent's work hours was not established.

This immediate cost reduction needs to be balanced against possible untreated case of true EONS, immediate morbidities like meningitis, ventriculitis and long-term outcomes like adverse neurodevelopment.

Equity (what would be the impact on health equity?)

Judgement: Probably increased

The impact on health equity would be variable. With the very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm. If the decreased usage of empiric antibiotics based on laboratory screening-based results versus immediate antibiotics in all at risk infants will decrease the immediate cost of care without substantial increase in mortality, relapse or long-term neurodevelopmental impairment, the intervention would increase health equity, as antibiotic therapy for neonatal sepsis would be more affordable for everybody. However, if lab test-based treatment increases mortality, untreated sepsis cases or long-term neurodevelopmental impairment, the intervention would reduce health equity, as substantially more cost and resources would be required to manage episodes of relapse and managing neurodevelopmental impairment. The equity of health care might increase as no drugs need to be purchased by parents/ caretakers at birth for asymptomatic at-risk neonates, and rooming-in can be done at birth for all the neonates so avoiding bed charges for neonates.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: Probably Yes

In view of inadequate evidence of the intervention on effect of mortality; recommendations for use of this intervention(antibiotic administration if a neonate is born with risk factors for sepsis develops symptoms) are probably yes for neonate born at ≥ 35 weeks of gestation and probably no for neonates born at < 35 weeks of gestation **.**Given avoiding the need for unnecessary intravenous cannulation and promoting rationale antibiotic administration and rooming-in of ≥ 35 weeks gestational age neonates with mothers, the intervention seems acceptable to all stakeholders. For <35 weeks gestational age

recommendations are probably No for following the intervention and treatment to be done as previously with empiric antibiotics for at risk neonates till sepsis is ruled out.

Feasibility (is the intervention feasible to implement?)

Judgement: Probably Yes

The intervention is feasible to implement considering the advantages offered to all stakeholders

RECOMMENDATION

6. For asymptomatic neonates born at or after 35 completed weeks of gestation and at risk¶ of early-onset sepsis, the guidelines group suggests administration of antibiotics *only* in the presence of positive laboratory markers of sepsis (such as, CRP, PCT or hematological parameters beyond age-appropriate cut-off values).

Weak recommendation, Low certainty of evidence

Justification

Overall justification

The evidence is derived from a study where neonates with gestation ≥ 35 weeks born to mothers receiving antibiotics for chorioamnionitis and routine GBS screening with intrapartum antibiotic prophylaxis. The panel needs to advise for laboratory testing with well-defined cut-offs and blood culture together with careful elucidation of risk factors like gestation, birth weight and clinical status of neonates. This approach should be coupled with monitoring in the immediate neonatal period for relapse and long-term neurodevelopmental outcomes.

The use of laboratory tests with well-defined cut-offs and screening strategy together with careful clinical monitoring will decrease the potential misuse of antibiotics.

Detailed justification

Desirable Effects

Reduction in antibiotic usage rates and more rationale usage of antibiotics, decreased hospital stay without any impact on in hospital mortality

Undesirable Effects

Possibility of missing potentially septic neonates at early stages hence delaying treatment, causing adverse outcome in form of meningitis, respiratory/ and cardiovascular failure and in worst case scenario causing mortality.

Subgroup considerations

As studies have looked at neonates with ≥35 wks gestation, hence guidelines can be applied to this subset and avoiding lower gestational ages as evidence in favour of recommendations at < 35 weeks doesn't exist.

Implementation considerations

Adequate number and quality of laboratory facilities need to be created uniformly across secondary and tertiary setups along with the building of standardized laboratory testing protocols.

Monitoring and evaluation

Careful formulation and dissemination of standardized testing protocols need to be established along with data recording preferably through a common digital platform of all high-risk neonates being managed with a said recommendation so that evidence can be strengthened and further refined for generalized applicability

Research priorities

Electronic data recording of all neonates being managed with the laboratory tests-based approach needs to be maintained rigorously and analysed periodically to assess its impact on neonatal mortality rate, duration of hospitalization and other important outcomes. Simultaneously the long-term outcome of these neonates in terms of readmission rates and survival until infancy needs to be accessed.

***Practice Question 7*: Among newborn infants with definite uncomplicated sepsis, is a short course of antibiotics (typically 5-7 days) non-inferior to a standard course of antibiotics (typically 10-14 days)?**

Pico question

P= Newborn infants with definite uncomplicated sepsis (bloodstream infection)
I= short course of intravenous antibiotics (typically 5-7 days)
C= standard course of intravenous antibiotics (typically 10-14 days)
O= mortality before discharge from hospital, mortality by day 28 of life, mortality by 12 months of corrected age, relapse with culture-positive sepsis or meningitis, relapse with culture-negative (suspected) sepsis or meningitis, duration of antibiotic therapy, duration of hospital stay, moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant for control, cerebral palsy, cognitive disability, blindness or deafness), death or moderate or severe neurodevelopmental impairment at or after 12 months of age.

Summary of evidence

Table 7 depicts the summary of evidence.

Table 7: Summary of findings

Patient or population: treatment of definite uncomplicated neonatal sepsis
Setting: all settings
Intervention: a short course of intravenous antibiotics (typically 5-7 days)
Comparison: a standard course of antibiotics (typically 10-14 days)

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with a standard course of antibiotics (typically 10-14 days)	**Risk with a short course of intravenous antibiotics (typically 5-7 days)**				
Mortality before discharge from hospital	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	
Mortality by day 28 of life	33 per 1,000	**11 per 1,000** (0 to 262)	**RR 0.33** (0.01 to 7.87)	60 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,b,c]	The evidence is very uncertain about the effect of a short course of intravenous antibiotics (typically 7-10 days) on mortality by day 28 of life.
Mortality by 12 months of corrected age	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	
Relapse with culture-positive sepsis or meningitis	0 per 1,000	**0 per 1,000** (0 to 0)	**RR 5.00** (0.25 to 100.32)	254 (3 RCTs)	⊕⊕⊕◯ MODERATE [c,d,e]	The evidence is very uncertain about the effect of a short course of intravenous antibiotics (typically 7-10 days) on relapse with culture-positive sepsis or meningitis.
Relapse with culture-negative (suspected) sepsis or meningitis	16 per 1,000	**26 per 1,000** (6 to 107)	**RR 1.67** (0.41 to 6.80)	254 (3 RCTs)	⊕⊕◯◯ LOW [c,f,g]	The evidence is very uncertain about the effect of a short course of intravenous antibiotics (typically 7-10 days) on relapse with culture-negative (suspected) sepsis or meningitis.

Duration of antibiotic therapy	The mean duration of antibiotic therapy was **0**	**0** (0 to 0)	-	(0 studies)	-	
Duration of hospital stay	The mean duration of hospital stay was **0** days	MD **3.62 days fewer** (4.4 fewer to 2.85 fewer)	-	188 (2 RCTs)	⊕⊕⊕◯ MODERATE [c,h]	A short course of intravenous antibiotics (typically 7-10 days) may reduce duration of hospital stay.
Moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness)	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	
Death or moderate or severe neurodevelopmental impairment at or after 12 months of age	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. Although the studies were not blinded, they have not been downgraded for lack of blinding because it would be practically difficult to blind this kind of intervention. Moreover, all-cause mortality is an outcome that does not have measurement bias. 2 of the studies (76, 77)(Chowdhary et al and Rohatgi et al) had some losses to follow up, which could potentially cause minimal attrition bias.
b. The width of the 95% confidence interval of RR was 0.01 to 7.87
c. The number of studies was too few to evaluate publication bias
d. Although the studies were not blinded, they have not been downgraded for lack of blinding because it would be practically difficult to blind this kind of intervention. Moreover, culture-positive sepsis is an outcome that has relatively less measurement bias (compared to culture negative sepsis). 2 of the studies (76, 77) (Chowdhary et al and Rohatgi et al) had some losses to follow up, which could potentially cause minimal attrition bias.
e. The width of the 95% confidence interval of RR was from 0.25 to 115.13
f. Downgraded for lack of blinding because culture-negative sepsis is a subjective outcome.
g. The width of the 95% confidence interval of RR was 0.41 to 6.80
h. Downgraded for lack of blinding because duration of hospitalization is a subjective outcome

Summary of judgements

Problem (is the problem a priority?)

Judgement: yes

Neonatal sepsis is an important cause of morbidity and mortality. Globally, neonatal sepsis accounts for 8% of all neonatal deaths in the 1st week of life and 37% of all deaths from the 2nd to 4th weeks of life (1). In hospital settings, the incidence of culture proven neonatal sepsis is 16 per 1000 live births in India(2). One large study from a rural community in India reported 4 cases of culture proven neonatal sepsis per 1000 live births (3). Population-based studies from India report highly variable incidences of clinically suspected sepsis- ranging from 4.6 to 170 per 1000 live births (4). Given the high incidence of sepsis, the use of antibiotics in the neonatal period is very high all over the world, particularly so in India.

The overuse and prolonged use of antibiotics, even in situations where it is not necessary, has resulted in an alarming problem of multidrug resistant neonatal sepsis. In South Asia, most isolates of Klebsiella pneumoniae, Escherichia coli and Acinetobacter baumannii are multidrug resistant(2). The reliance on newer generations of antibiotics has also increased the cost of care and the incidence of serious adverse events. In view of these problems, it is important to optimise the duration of antibiotic therapy, so that longer courses of antibiotics are not administered where shorter courses would do the job. If shorter courses of antibiotics are found to be as efficacious as standard courses, without any increased risk of relapses, complications, or mortality, then shorter courses could safely replace longer courses.

Shorter courses of antibiotics would be expected to cause less serious adverse events, require shorter hospitalisation, incur less cost and decrease the risk of secondary bacterial infections. When scaled up to the level of the community, the benefits, if any, of shorter courses of antibiotics would be enormous, resulting in many more hospital beds being freed up, and less financial burden on the public health system.

There is no consensus in clinical practice regarding the optimal duration of antibiotic therapy for culture proven neonatal sepsis. Pediatric and neonatology textbooks mention figures between one week and two weeks of therapy, with most units prescribing 10-14 days of antibiotics for culture proven uncomplicated neonatal septicemia. In a survey conducted by the panellists, the comparison of a short course of antibiotics versus a standard course of antibiotics for uncomplicated culture proven bacterial sepsis among neonates was rated to be extremely important.

In view of all the above facts, this problem is considered a priority.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: varies

The important desirable effects with short course of antibiotics at the level of the individual patient are shorter duration of hospitalization and antibiotic therapy; and at the level of the healthcare facility are decrease in the incidence of MDR, XDR and PDR, and decrease in the incidence of fungal sepsis.

Two randomized controlled trials reported on duration of hospitalization (75, 76). Quality of evidence was low because of the serious risk of bias. The absolute effect on duration of hospitalization ranged from 2.85 to 4.4 fewer days of hospitalization with short course of antibiotics. Although no randomized controlled trials reported on the actual duration of antibiotic therapy, it can be surmised that subjects receiving a short course of antibiotics would have fewer days of antibiotics compared to those receiving a standard course.

The panel did not *a priori* plan to assess the decrease in the incidence of MDR, XDR and PDR bacterial and fungal sepsis in the healthcare facility, as these outcomes can only be

compared in a before and after study design, or in large cluster-randomized trials or after short course of antibiotics is implemented in the unit as a policy for all infants. Nevertheless, during the literature search, none of the studies reported on these outcomes.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: varies

Critically important undesirable effects are mortality (before hospital discharge, by day 28 of life and by 12 months of post-term corrected age), moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and death or moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and relapse with culture-positive sepsis or meningitis. The important effect is relapse with suspected (culture-negative) sepsis or meningitis.

There were no randomized controlled trials addressing the outcomes of death before hospital discharge, death by 12 months of post-term corrected age, moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age, death or moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and duration of antibiotic therapy. 3 randomized controlled trials reported on mortality by day 28 of life (75-77). Quality of evidence was low because of serious imprecision. The absolute effect on mortality by day 28 of life ranged from 33 fewer deaths to 229 more deaths per 1000 subjects. The risk estimates are imprecise and include no effect, substantial benefit, and substantial harm.

3 randomized controlled trials reported on relapse with culture-positive sepsis or meningitis, and relapse with suspected (culture-negative) sepsis or meningitis (75-77). Quality of evidence for relapse with culture-positive sepsis or meningitis was low because of serious imprecision. The absolute effect on relapse with culture-positive sepsis or meningitis ranged from 20 fewer to 50 more culture positive relapses per 1000 subjects. Quality of evidence for relapse with culture-negative sepsis or meningitis was very low because of serious risk of bias and serious imprecision. The absolute effect on probable relapse with culture-negative sepsis meningitis ranged from 14 fewer to 137 more relapses per 1000 subjects. The risk estimates are imprecise and include no effect, substantial benefit, and substantial harm.

In one randomized controlled trial, the subgroup analysis of *Staphylococcus aureus* septicemia showed a statistically significantly increased relapse rate with a shorter duration of antibiotics.

Certainty of evidence (what is the overall certainty of the evidence of effects?)

Judgement: low

The overall certainty of the evidence of effects is low. There is no evidence available for most of the critical outcomes, barring mortality by day 28 and relapse with culture-positive sepsis or meningitis. Only 2 randomised controlled trials addressed one important desirable outcome (duration of hospitalisation) and 3 randomized controlled trials addressed two critical undesirable outcomes (mortality by day 28 and culture positive relapse) and one important undesirable outcome (relapse with culture-negative sepsis or meningitis). For the critical and important undesirable outcomes, the risk estimates were imprecise and the 95% CI limits around the pooled estimate included no effect, and substantial benefit and substantial harm.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: no important uncertainty or variability

A shorter course of antibiotics should ideally be non-inferior to a standard course of antibiotics. The benefit with shorter course would be shorter duration of antibiotics,

hospitalization, lower cost, less adverse effects, less discomfort and pain, provided there is no increase in undesirable effects such as mortality, relapse or a neurodevelopmental impairment. Although these outcomes would be weighed against each other, more value would be given to mortality, relapse, and neurodevelopmental impairment. In the absence of good quality evidence to show that shorter courses are not inferior to standard courses with respect to mortality, relapse and neurodevelopmental impairment, it would not be possible to recommend shorter courses solely on the basis of shorter duration of antibiotics, shorter hospitalization and so on.

The guideline panel considers that there is no important uncertainty of variability in how much physicians, parents, policymakers or public health experts would value the main outcomes, i.e. mortality at various time points and moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and definite relapse of culture proven sepsis or meningitis. There can be no 2 opinions about the critical importance of avoiding preventable deaths. Moderate to severe neurodevelopmental impairment poses a substantial and lifelong burden on the family, hospitals, the health system, and society (78). Thus, the panel believes neurodevelopmental impairment is also a universally acknowledged critically important outcome. Relapses with culture proven sepsis necessitate re-hospitalization, painful procedures, re-exposure to antibiotics and the risk of superinfections. Thus, avoiding relapses is important from the point of view of all stakeholders.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: does not favour either the intervention or the comparison

The balance between desirable and undesirable effects does not favour either the intervention of the comparison. There was no serious risk of bias, inconsistency or indirectness with respect to the 2 critical outcomes measured; whereas, there was serious risk of bias but no serious inconsistency or indirectness with respect to the 2 important outcomes. All outcomes, both critical and important, had serious imprecision. 95% confidence limits of the absolute effects of a short course of antibiotics includes no effect, substantial benefit and substantial harm for all the critical outcomes evaluated. Overall, there is a paucity of evidence and literature, with only 3 small randomised controlled trials addressing the issue, and several critically important outcomes remaining unaddressed.

Resources required (*How large are the resources required?)*

Judgement: moderate savings

There is low quality evidence that a shorter course of antibiotics may result in a shorter duration of hospitalisation. Although none of the trials have reported a cost calculation, it may be inferred that there would be a modest saving because of lower direct and indirect costs of occupying a hospital bed. Although none of the trials had reported on the actual duration of antibiotic therapy, it is almost self-evident that shorter duration of antibiotics would cost less than standard duration of antibiotics. Thus, shorter duration of antibiotics may reduce costs in the short term.

It is not possible to comment whether short duration of antibiotics will reduce costs in the long term. With the current state of evidence available from literature, the balance of effects does not favour either a short course of antibiotics or a standard course for the critically important outcomes. Since substantial harm in the form of moderate to severe neurodevelopmental impairment (which would require increased cost of care) and definite relapse (which would require re-hospitalisation and re-treatment) cannot be excluded, the possible short-term cost savings may be nullified in the long run.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: no included studies

Shorter duration of antibiotics and lesser days of hospitalization are expected to decrease costs. However, none of the included randomized controlled trials reported a cost calculation. A wide variety of antibiotics and paraphernalia for the administration of antibiotics are used in the treatment of neonatal sepsis. The per day cost of a hospital bed is also extremely variable, depending upon the level of care. Therefore, it is difficult to simulate the expected difference in cost of care.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: does not favour either the intervention of the comparison

Cost effectiveness was not studied in any of the randomized controlled trials. The cost effectiveness of the intervention does not favour either the intervention or the comparison because, apart from a modest decrease in the duration of hospitalization, the quality of evidence for all critically important and important outcomes is very low, and the effect includes both substantial benefit and substantial harm. The issue of cost effectiveness would arise only if it was possible to conclude that the intervention provides at least some benefit for critical outcomes.

Equity (what would be the impact on health equity?)

Judgement: varies

The impact on health equity would be variable. With the very low quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm. In the event that the truth is that short course of antibiotics reduces the duration of antibiotic therapy and duration of hospitalisation without substantial increase in mortality, relapse or long-term neurodevelopmental impairment, the intervention would increase health equity, as antibiotic therapy for neonatal sepsis would be more affordable for everybody. However, in the event the short course of antibiotics increases mortality, relapse or long-term neurodevelopmental impairment, the intervention would reduce health equity, as substantially more cost and resources would be required to manage episodes of relapse and managing neurodevelopmental impairment.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: varies

With the low quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm. In this context, the acceptability of short course of antibiotics would vary between the key stakeholders.

Feasibility (is the intervention feasible to implement?)

Judgement: yes

Per se, the intervention (short course of antibiotics) is very feasible to implement because it requires less resources. However, the issue of feasibility does not arise at present. With the low quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm with either the short course or standard course of antibiotics.

RECOMMENDATION

7. The guidelines group suggests NOT to use a shorter course of intravenous antibiotics (typically 5-7 days) in the management of neonates with uncomplicated@ and definite (i.e., culture-positive) neonatal sepsis; these neonates may preferably be treated with the standard course of antibiotics (typically 10-14 days).

Weak recommendation, Low certainty of evidence

@ Uncomplicated sepsis defined as any condition that is NOT treated with more than 10-14 days of antibiotics as per current standards of care, e.g., CNS infections, bone and joint infections, deep-seated abscesses

Justification

Overall justification

Although there is no prescribed standard of care currently, most units tend to prescribe antibiotics for 10-14 days for definite neonatal sepsis, and over the years this has become default duration, despite the lack of evidence to back it. Therefore, in the view of this panel, to shorten the duration of antibiotics, it would be necessary to demonstrate that shorter duration of antibiotics is not inferior to the standard duration with respect to mortality, relapse rates and neurodevelopmental impairment. Since the evidence in literature is inconclusive about these critical outcomes, any kind of recommendation in favour of the intervention (short course) it is not possible. Considering that the evidence is inconclusive and there is weak evidence in favor of shorter duration of hospitalization, the panel decided to make a weak recommendation against the intervention. One of the 3 randomized controlled trials reported a significantly higher relapse rate amongst neonates infected with *Staphylococcus aureus* (77). Therefore, the panel made a strong recommendation against the use of short courses of antibiotics in the context of *Staphylococcus aureus* septicemia.

Detailed justification

Desirable Effects

The quality of evidence for the duration of hospitalization is low. There is a serious risk of bias and serious imprecision.

Undesirable Effects

Critical outcomes such as mortality, definite culture proven relapse of sepsis/meningitis, and moderate to severe neurodevelopmental impairment had serious imprecision.

Certainty of evidence

Evidence was of very low quality

Subgroup considerations

No subgroup analyses were performed

Implementation considerations

The panel suggests not administering a short course of antibiotics for bacteriologically proven neonatal sepsis. If, at a future date, if evidence emerges that short course antibiotic therapy is associated with substantially greater benefit than harm, then implementation of short course antibiotic therapy is unlikely to require any special prerequisites, training, infrastructure or expenditure.

Investigators in 2 out of the 3 randomized controlled trials that were considered, had included a C-reactive protein test on the day the short course of antibiotics was completed (75, 76). If short-course antibiotics are ever implemented, an extra C-reactive protein test may have to be considered.

Monitoring and evaluation

Since the panel suggests not administering short-course antibiotics, there is no extra monitoring or evaluation that needs to be done, over and above what is currently being done.

Research priorities

Given the paucity of evidence, the panel recommends that large multi-centric non-inferiority open-label, randomised controlled trials must be conducted to compare shorter courses of antibiotics versus standard courses of antibiotics in uncomplicated, culture proven neonatal bacterial septicemia.

***Practice Question 8*: Among newborn infants with uncomplicated probable septicemia or pneumonia (culture negative), is 2-3 days of intravenous antibiotics non-inferior to standard 5-7 days course of intravenous antibiotics?**

Pico question

P= Neonates with uncomplicated probable neonatal septicemia or pneumonia
I= a short course of antibiotics (typically 4 days)
C= standard 5-7 days course of intravenous antibiotics
O= Mortality during hospital stay; Mortality by 28 days of life; Mortality by 12 months corrected age; Death or moderate or severe neurodevelopmental impairment at or after 12 months of corrected age; Relapse within one month with culture proven/ probable sepsis or meningitis; Relapse within one month with culture proven sepsis or meningitis; Duration of Hospitalization; Cost of antibiotics

Background

Neonatal sepsis is an important cause of morbidity and mortality. Globally, neonatal sepsis accounts for 8% of all neonatal deaths in the 1st week of life and 37% of all deaths from the 2nd to 4th weeks of life (1). Additionally, pneumonia in the neonatal age group annually adds around one million deaths and many stillbirths globally (79). Furthermore, the case fatality rates of sepsis in neonates are very high. Neonatal sepsis is associated with non-specific signs and symptoms. Especially in early stages of sepsis and in preterm population, it is very difficult to differentiate signs of infection from non-infectious phenomena. Therefore, empiric antibiotics are promptly initiated in presence of signs and symptoms suggestive of sepsis. However, prolonged, and unnecessary use of antibiotics lead to harmful effects on the host as well as

on the environment. Conventionally the duration of therapy is empirical and is not subjected to rigorous clinical trials (80).We review the evidence for optimal duration of antibiotic therapy in neonates with suspected sepsis, and pneumonia. We hypothesize that a shorter course of antibiotics (typically 3-4 days) would be as good as conventional 5-7 days of intravenous antibiotics for the management of probable neonatal sepsis and/or pneumonia.

Summary of evidence

Table 8 shows the summary of evidence.

Table 8: Summary of findings

Patient or population: the treatment of uncomplicated probable neonatal sepsis or pneumonia
Intervention: a short course of antibiotics (typically 4 days)
Comparison: standard 5-7 days course of intravenous antibiotics

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard 5-7 days course of intravenous antiobiotics	**Risk with a short course of antibiotics (typically 4 days)**				
Mortality during hospital stay	0 per 1,000	**0 per 1,000** (0 to 0)	Outcome not estimatable	70 (1 RCT)	⨁⨁◯◯ Low[a,b,c,d]	Only one study reported this outcome and there were no events in any of the groups. It is not possible to comment whether there is any difference in mortality by 28 days between short course (4 days) and standard (5-7 days) intravenous antibiotic therapy for probable neonatal sepsis or pneumonia.
Mortality by 28 days of life follow-up: range 1 days to 28 days	0 per 1,000	**0 per 1,000** (0 to 0)	Outcome not_estimatable	70 (1 RCT)	⨁⨁◯◯ Low[a,b,c,d,e]	Only one study reported this outcome and there were no events in any of the groups. It is not possible to comment whether there is any difference in mortality by 28 days between short course (4 days) and

						standard (5-7 days) intravenous antibiotic therapy for probable neonatal sepsis or pneumonia.
Mortality by 12 months corrected age - not reported	-	-	-	-	-	No study reported this outcome
Death or moderate or severe neurodevelopmental impairment at or after 12 months of corrected age - not reported	-	-	-	-	-	No study reported this outcome
Relapse within one month with culture proven/ probable sepsis or meningitis follow-up: range 1 days to 30 days	2 per 100	**2 per 100** (0 to 17)	**RR 1.45** (0.19 to 10.94)	255 (4 RCTs)	⊕◯◯◯ Very low[c,d,e,f]	There was no significant difference in relapse rates of culture-proven or probable sepsis or meningitis within one month after completion of antibiotics between short course (4 days) and standard (5-7 days) intravenous antibiotic therapy for probable neonatal sepsis or pneumonia.
Relapse within one month with culture proven sepsis or meningitis follow-up: range 1 days to 30 days	17 per 1,000	**3 per 1,000** (0 to 64)	**OR 0.19** (0.01 to 4.06)	237 (4 RCTs)	⊕⊕◯◯ Low[a,f,g,h]	There was no significant difference in relapse rates with culture proven sepsis or meningitis within one month after completion of antibiotics between short course (4 days) and standard (5-7 days) intravenous antibiotic therapy for probable neonatal sepsis or pneumonia.

Duration of Hospitalization	The mean duration of Hospitalization was **0**	MD **2.1 lower** (2.19 lower to 2.01 lower)	-	143 (2 RCTs)	⊕◯◯◯ Very low[b,d,f,g,i]	Short course (4 days) may reduce the duration of hospitalization as compared to standard (5-7 days) intravenous antibiotic therapy for probable neonatal sepsis or pneumonia.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **OR:** odds ratio; **RR:** risk ratio

Explanations
a. Although the studies were not blinded, they have not been downgraded for lack of blinding because it would be practically difficult to blind this kind of intervention. Additionally, measurement bias is not applicable to this outcome.
b. The results are largely applicable to late preterm and term neonates as three out of four studies (except Saini et al) enrolled neonates >34 weeks and Saini et al enrolled >30 weeks.
c. Overall the pooled estimate had small sample size, small event rates and wide confidence interval
d. The number of studies was too few to evaluate publication bias
e. Downgraded by one step for lack of blinding as there is a risk of ascertainment bias for probable sepsis
f. Study by Pasha et al and Saini et al followed neonates for 14 days after stopping antibiotics. Engle et al followed for 2-3 days after stopping antibiotics.
g. The event rate is very small, only one study reported it. It is difficult to comment on consistency
h. The outcome was rare. Therefore, the precision is limited for this outcome
i. Downgraded by one step for lack of blinding as there is a risk of ascertainment bias for Duration of hospitalization

Summary of judgements

Problem (is the problem a priority?)

Judgement: Yes

Sepsis is the third most common cause of mortality among neonates (81) .Neonatal sepsis is associated with numerous morbidities including respiratory failure, shock, acute kidney injury, bleeding manifestations, and central nervous dysfunction. In premature neonates, sepsis is also associated with medium term complications such as periventricular leukomalacia, retinopathy of prematurity, bronchopulmonary dysplasia, and necrotising enterocolitis. Therefore, sepsis and its morbidities can have detrimental impact on long-term neurodevelopmental outcomes in neonates. In a recent meta-analysis of studies reporting neonatal sepsis among hospital settings from south Asian countries, the incidence of culture-proven neonatal sepsis was found to be 15.7 (95% confidence interval: 12.7 to 18.8) per 1000 live births (2).The case fatality rate of neonatal sepsis amongst these studies was 34.4% (95% confidence interval: 33.1 to 35.6). High incidence of sepsis in developing countries, high case fatality rates and risk of morbidities have led to overuse use of antibiotics.

The conventional duration of antibiotics therapy in probable neonatal sepsis is 7 days. This duration of antibiotic therapy is empirical and is not evidence based. The overuse of antibiotics due to above-said concerns might lead to prolonged hospitalization leading to increased cost of care, unnecessary intravenous catheterization, painful interventions, mother-infant separation, increased colonization by pathogenic organisms and emergence of drug-resistant strains (80) .The alarming rise of multidrug and even extensive drug-resistant organisms is a real concern in current neonatal medicine. In South Asia, most isolates of *Klebsiella pneumoniae, Escherichia coli* and *Acinetobacter baumannii* are multidrug resistant (2). In view of these

problems, there is an urgent need to optimize the duration of antibiotic therapy for probable sepsis to avoid overuse of antibiotics. In view of all the above facts, this problem is considered a priority.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: Varies

The important patient-centric desirable effects with short course of antibiotics are shorter duration of hospitalization and cost of therapy. Two randomized controlled trials reported on duration of hospitalization (79, 82). Short course of antibiotics resulted in decrease in duration of hospitalization by 2.10 days [95% CI -2.19, -2.01] as compared to standard course. The quality of evidence was low because of the serious risk of bias. Although no randomized controlled trials reported on the actual duration of antibiotic therapy, it can be surmised that subjects in the short course antibiotics arms would have fewer days of antibiotics compared to those receiving a standard course. The desirable effects at the level of the healthcare facility are decrease in the incidence of MDR, XDR and PDR and decrease in the incidence of fungal sepsis. The panel did not a priori plan to assess the decrease in the incidence of MDR, XDR and PDR bacterial and fungal sepsis in the healthcare facility, as these outcomes can only be compared in a before and after study design, or in large cluster-randomized trials or after short course of antibiotics is implemented in the unit as a policy for all infants. Nevertheless, during the literature search, none of the studies reported on these outcomes.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: Varies

Critically important undesirable effects are mortality (before hospital discharge, by day 28 of life and by 12 months of post-term corrected age), moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age, death or neurodevelopmental (moderate to severe) impairment by 12 months of post-term corrected age, and relapse with culture-positive sepsis or meningitis. The important effect is relapse with suspected (culture-negative) sepsis or meningitis. There were no randomized controlled trials addressing the outcomes of death by 12 months of post-term corrected age, death or moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age. Only one of four included randomized controlled trials reported on mortality by hospital discharge and mortality by 28 days of life (79) .The quality of evidence was low because of serious risk of imprecision and indirectness. In a single study which reported death by hospital discharge and till 28 days of life, there were no events reported in 70 randomized neonates. Therefore, it is not possible for the review group to consider this outcome for giving recommendation in favour or against the short course. The risk estimates appear imprecise and include no effect, substantial benefit, and substantial harm. Four randomized controlled trials reported on relapse with culture-positive sepsis or meningitis, and relapse with culture-proven or suspected (culture-negative) sepsis or meningitis (79, 80, 82, 83). Quality of evidence was low (elapse with culture-positive sepsis or meningitis) to very low (culture-proven or suspected (culture-negative) sepsis or meningitis) because of serious risk of bias, imprecision as well as indirectness. The relative risk of relapse with either culture-positive, probable sepsis or meningitis was not significant as the 95% confidence interval ranged from 0.2 to 10.9. The relative risk of relapse with culture-positive sepsis or meningitis was also not significant as the 95% CI ranged from 0.01 to 4.06. The risk estimates are imprecise and include no effect, substantial benefit, and substantial harm.

Certainty of evidence (what is the overall certainty of the evidence of effects?)

Judgement: Very low

The overall certainty of the evidence of effects is low to very low. Out of five critical outcomes, there is no evidence available for 2 critical outcomes (Death by 12 months corrected age, Death or moderate to severe neurodevelopmental impairment at or after 12 months of age), as these were not evaluated by any study. Two critical outcomes i.e. death during hospital stay and death by 28 days of life were reported by a single study in small sample of 70 neonates (79).All four included randomized trials reported one critical outcome i.e. relapse with culture positive sepsis or meningitis within one month. There were two events observed for this outcome in the standard 5-7 days group, and the pooled estimate included no effect, substantial benefit, and substantial harm. Two randomized controlled trials (79, 82) addressed an important desirable outcome (duration of hospitalization), for which the 95% confidence interval limits around the pooled estimate showed substantial benefit. However, the certainty of the evidence was very low due to serious risk of bias, indirectness, and imprecision. For other desirable outcome i.e., relapse with culture positive or probable sepsis or meningitis within one month, there were two events observed for this event in standard 5-7 days group, however their risk estimates were imprecise, had serious risk of bias, and had indirectness. The pooled estimate included significant harm, no effect and significant benefit.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: No important uncertainty or variability

A shorter course of antibiotics should ideally be non-inferior to a standard course of antibiotics with respect to undesirable effects such as mortality, relapse, or a neurodevelopmental impairment and superior with respect to duration of antibiotics, duration of hospitalization, and cost of therapy. Although these outcomes would be weighed against each other, more value would be given to mortality, relapse, and neurodevelopmental impairment. In the absence of good quality evidence to show that shorter courses are not inferior to standard courses with respect to mortality, relapse, and neurodevelopmental impairment, it would not be possible to recommend shorter courses solely based on shorter duration of antibiotics, shorter hospitalization and so on.

The guideline panel considers that there is no important uncertainty of variability in how much physicians, parents, policymakers, or public health experts would value the main outcomes, i.e., mortality at various time points and moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and definite relapse of culture proven sepsis or meningitis. There can be no 2 opinions about the critical importance of avoiding preventable deaths. Moderate to severe neurodevelopmental impairment poses a substantial and lifelong burden on the family, hospitals, the health system, and society (78) .Thus, the panel believes neurodevelopmental impairment is also a universally acknowledged critically important outcome. Relapses with culture proven sepsis necessitate rehospitalisation, painful procedures, re-exposure to antibiotics and the risk of superinfections. Thus, avoiding relapses is important from the point of view of all stakeholders.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: Does not favour either the intervention or the comparison

The balance between desirable and undesirable effects does not clearly favor short course or standard course of antibiotics. Evidence both for the desirable as well as the undesirable effects of a short course of antibiotics is of very low quality because of serious risk of bias and

very serious imprecision. 95% confidence limits of the absolute effects of a short course of antibiotics includes no effect, substantial benefit, and substantial harm for all the critical outcomes evaluated. Overall, there is a paucity of evidence and literature, with only 4 small randomized controlled trials addressing the issue, and several critically important outcomes remaining unaddressed.

Resources required (*How large are the resources required?)*

Judgement: Moderate savings

There is low quality evidence that a shorter course of antibiotics may result in a shorter duration of hospitalization. Although none of the trials have reported a cost calculation, it may be inferred that they would be a modest saving because of lower direct and indirect costs of occupying a hospital bed. Although none of the trials had reported on the actual duration of antibiotic therapy, it is almost self-evident that shorter duration of antibiotics would cost less than standard duration of antibiotics. Thus, shorter duration of antibiotics may reduce costs in the short term.

It is not possible to comment whether short duration of antibiotics will reduce costs in the long term. With the current state of evidence available from literature, the balance of effects does not favour either a short course of antibiotics or a standard course for the critically important outcomes. Since substantial harm in the form of moderate to severe neurodevelopmental impairment (which would require increased cost of care) and definite relapse (which would require re-hospitalization and re-treatment) cannot be excluded, the possible short-term cost savings may be nullified in the long run.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: No included studies

Shorter courses of antibiotics are likely to be associated with shorter duration of hospitalization and are expected to decrease costs. However, none of the included randomized controlled trials reported a cost calculation. A wide variety of antibiotics and paraphernalia for the administration of antibiotics are used in the treatment of neonatal sepsis. The per day cost of a hospital bed is also extremely variable, depending upon the level of care. Therefore, it is difficult to simulate the expected difference in cost of care

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: Does not favour either the intervention or the comparison

Overall, there is uncertainty about the beneficial effects of the short course of antibiotics for probable neonatal sepsis or pneumonia. Additionally, cost effectiveness was not studied in any of the randomized controlled trials. Furthermore, the quality of evidence for all critically important and important outcomes is very low, and the effect includes both substantial benefit and substantial harm. Therefore, the cost effectiveness of the intervention does not favour either the intervention or the comparison.

Equity (what would be the impact on health equity?)

Judgement: Varies

The impact on health equity would be variable. With the small number of studies and very low event rates it was not possible to check effectiveness separately for various subgroups i.e., probable sepsis, /pneumonia, high-income/low-income settings. With the currently available

low to very low-quality evidence, it is not possible to exclude substantial benefit or substantial harm overall as well as in subgroups.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: Varies

With the low to very low-quality evidence currently available, it is not possible to exclude the substantial benefits or substantial harms. In this context, the acceptability of short course of antibiotics would vary between the key stakeholders.

Feasibility (is the intervention feasible to implement?)

Judgement: Probably yes

It is possible to implement the intervention, but it is difficult to sustain the intervention based on the pooled estimates of RCTs. With low to very low-quality evidence currently available, it is not possible to exclude substantial benefits or substantial harms with either the short course or standard course of antibiotics. The barriers of uncertainty can be overcome by following means (if this intervention is implemented): close follow-up of neonates in hospital settings for next 2-3 days after short course, and utilization of laboratory markers to decrease the uncertainty. The other alternative is to perform a large, adequately powered randomized controlled trial to address this issue.

RECOMMENDATION

8. The guideline group suggests NOT to use a shorter course of antibiotics (typically 2-3 days) for the treatment of uncomplicated@ probable neonatal sepsis or pneumonia; these neonates may preferably be treated with the standard 5-7 days course of intravenous antibiotics.

Weak recommendation, Very low certainty of evidence

@ Uncomplicated sepsis defined as any condition that is NOT treated with more than 10-14 days of antibiotics as per current standards of care, e.g., CNS infections, bone and joint infections, deep-seated abscesses

Justification

Overall justification

The current standard of care i.e., prescribing 5-7 days of intravenous antibiotics is empirical and is not evidence based. Over the years, it has become default intervention despite the lack of evidence to back it. However, the uncertainty of the clear beneficial or harmful effects between the short-course and the standard-course of antibiotic therapy is evident after the review. Therefore, in view of this panel, it would be necessary to demonstrate that the shorter duration of antibiotics is not inferior to the standard duration with respect to the mortality, relapse rates and neurodevelopmental impairment to shorten the duration of antibiotics. Considering that the evidence is inconclusive, the panel decided on a weak recommendation against the short course of antibiotics for the treatment of uncomplicated probable neonatal sepsis or pneumonia.

Detailed justification

Desirable Effects

The desirable effect is lesser duration of hospitalization however, the quality of evidence for is low.

Undesirable Effects

The quality of evidence for critical outcomes such as mortality and mortality or moderate to severe neurodevelopmental impairment was low because of serious imprecision and inconsistency. The quality of evidence for critical outcomes such as relapse of definite culture-proven sepsis/meningitis was low because of serious inconsistency and imprecision.

Certainty of evidence

Evidence was of low to very low quality

Subgroup considerations

No subgroup analyses were performed

Implementation considerations

The panel gives a weak recommendation against the short course of antibiotics for probable neonatal sepsis or pneumonia based on the current evidence.

Monitoring and evaluation

Since the panel gives a weak recommendation against the intervention (short-course antibiotics) and suggests continuation of the standard (5-7 days) course of antibiotics, there is no extra monitoring or evaluation that needs to be done, over and above what is currently being done. However, if any unit deviates from the current recommendations the safety of the neonates can be increased by following means: close follow-up of neonates in hospital setting for next 2-3 days after completion of antibiotics, and utilization of negative predictive values of acute phase reactants.

Research priorities

Given the paucity of evidence, the panel recommends undertaking non-inferiority, randomized controlled trials (preferably blinded) to compare shorter courses of antibiotics versus standard courses of antibiotics in uncomplicated, probable neonatal sepsis or pneumonia.

***Practice Question* 9: Among newborn infants with definite uncomplicated sepsis, is stoppage of intravenous antibiotics guided by biomarker turning negative (e.g. CRP, PCT) non-inferior to a standard 10-14 days course of intravenous antibiotics?**

Pico question

P= Uncomplicated probable neonatal sepsis
I= Stopping intravenous antibiotics after biomarker turning negative
C= A standard 5-7 day antibiotics therapy
O= Mortality during hospital stay; Mortality by 28 days of life; Death or moderate or severe neurodevelopmental impairment at or after 12 months of corrected age; Relapse within one month with culture proven/ probable sepsis or meningitis; Relapse within one month with culture proven sepsis or meningitis; Duration of Hospitalization

Background

Neonatal sepsis is an important cause of morbidity and mortality. Globally, neonatal sepsis accounts for 8% of all neonatal deaths in the 1st week of life and 37% of all deaths from the 2nd to 4th weeks of life (1). Furthermore, the case fatality rates of sepsis in neonates are very high. Neonatal sepsis is associated with non-specific signs and symptoms. Especially in early stages of sepsis and in preterm population, it is very difficult to differentiate signs of infection from non-infectious phenomena. Therefore, empiric antibiotics are promptly initiated in presence of signs and symptoms suggestive of sepsis. However, prolonged and unnecessary use of antibiotics lead to harmful effects on the host as well as on the environment (80). Conventionally, the duration of therapy is administered for 5-7 days in neonates suffering from probable neonatal sepsis and is not subjected to rigorous clinical trials. Alternatively, biomarkers can guide the duration of antibiotics in such neonates as the antibiotics can be stopped early if the biomarkers turn negative during antibiotic therapy. We review the evidence for antibiotic duration guided by biomarker turning negative vs standard 5-7 days of intravenous antibiotic therapy in neonates with probable sepsis. We hypothesize that antibiotic duration guided by biomarker would lead to reduction in the duration of antibiotic therapy without increasing the undesirable outcomes as compared to the conventional 5-7 days of intravenous antibiotics for the management of probable neonatal sepsis.

Summary of evidence

Table 9 shows the summary of evidence.

Table 9: Summary of findings

Patient or population: uncomplicated probable neonatal sepsis
Setting: all settings
Intervention: Stoppage of intravenous antibiotics by biomarker turning negative
Comparison: standard 5-7 days antibiotics therapy

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard 5-7 days antibiotics therapy	**Risk with Stoppage of intravenous antibiotics by biomarker turning negative**				
Mortality during the hospital stay - not reported	-	-	-	-	-	No study reported the death till hospital discharge
Mortality within day 30 of life follow-up: range 1 days to 30 days	1 per 1,000	**0 per 1,000** (0 to 10)	**RR 0.32** (0.01 to 7.96)	1512 (3 RCTs)	⨁⨁◯◯ Low[a,b,c,d]	Due to very less event rate of this outcome, we cannot comment whether there is any difference in mortality within 30 days of life between biomarker guided therapy and standard 5-7 days antibiotic therapy for probable neonatal sepsis.
Mortality by 12 months of corrected age - not reported	-	-	-	-	-	No study has analyzed this outcome
Death or moderate or severe neurodevelopmental impairment (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness) at or after 12 months of age - not reported	-	-	-	-	-	No study has analyzed this outcome

Relapse of culture-proven/probable sepsis or meningitis follow-up: range 1 days to 30 days	7 per 1,000	**14 per 1,000** (4 to 45)	**RR 1.98** (0.59 to 6.47)	1512 (3 RCTs)	⊕◯◯◯ Very low[b,c,d,e]	Biomarker guided therapy appears to have similar relapse rates of proven or probable sepsis within a month of stopping antibiotics as compared to standard 5-7 days of antibiotics.
Relapse with culture proven sepsis or meningitis	1 per 1,000	**1 per 1,000** (0 to 12)	**RR 0.37** (0.02 to 8.75)	1512 (3 RCTs)	⊕⊕◯◯ Low[a,b,c,d]	Due to very less event rate of this outcome, we cannot comment whether there is any difference in relapse with proven sepsis or meningitis between biomarker guided therapy and standard 5-7 days antibiotic therapy for probable neonatal sepsis.
Duration of Antibiotic therapy	-	SMD **0.22 SD lower** (0.31 lower to 0.13 lower)	-	1814 (3 RCTs)	⊕◯◯◯ Very low[c,d,e,f]	The evidence suggests that the biomarker-guided antibiotic therapy (stopping intravenous antibiotics after biomarker turning negative) reduces duration of antibiotic therapy in comparison to the standard 5-7 days of intravenous antibiotics for probable neonatal sepsis.
Duration of Hospitalization		MD **0.2 lower** (0.76 lower to 0.36 higher)	-	1710 (1 RCT)	⊕◯◯◯ Very low[a,b,c,g]	There was no significant difference in the duration of hospitalization between biomarker guided therapy and standard 5-7 days antibiotic therapy for probable neonatal sepsis.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **MD:** mean difference; **RR:** risk ratio; **SMD:** standardised mean difference

Explanations
a. Although the studies were not blinded, they have not been downgraded for lack of blinding because it would be difficult to blind this kind of intervention. Moreover, the outcome is not affected by measurement bias. Although Ehl et al and Numbenjapon et al did not clarify the allocation concealment, it was ignored as their sample size contribution to the pooled estimate was not significant.
b. The event rate is very low, and the outcome has a very wide confidence interval
c. The number of studies was too few to evaluate publication bias

d. Stocker et al enrolled neonates with gestational age >34 weeks. Moreover, nearly 40% of enrolled neonates had 'infection unlikely' as defined by the authors. In study by Ehl et al, 6 infants from group 2a (biomarker-guided), and seven infants from group 2b (standard therapy) were culture positive in the beginning.
e. The outcome has been downgraded for lack of blinding as the outcome of probable sepsis is subjected to measurement bias.
f. The outcome has a wide confidence interval
g. This outcome was reported only by Stocker et al. They enrolled neonates with gestational age >34 weeks and over 40% of enrolled neonates had 'infection unlikely' as defined by the authors.

Summary of judgements

Problem (is the problem a priority?)

Judgement: Yes

Sepsis is the third most common cause of mortality among neonates (81). Neonatal sepsis is associated with numerous morbidities including respiratory failure, shock, acute kidney injury, bleeding manifestations, and central nervous dysfunction. In premature neonates, sepsis is also associated with medium term complications such as periventricular leukomalacia, retinopathy of prematurity, bronchopulmonary dysplasia, and necrotising enterocolitis. Furthermore, sepsis and its morbidities can have detrimental impact on long-term neurodevelopmental outcomes in neonates. In a recent meta-analysis of studies reporting neonatal sepsis in hospital setting (from south Asian countries), the incidence of culture-proven neonatal sepsis was found to be 15.7 (95% confidence interval: 12.7 to 18.8) per 1000 live births (2). The case fatality rate of neonatal sepsis amongst these studies was 34.4% (95% confidence interval: 33.1 to 35.6). High incidence of sepsis in developing countries, high case fatality rates and risk of morbidities in neonatal sepsis have led to the overuse of antibiotics.

Conventionally antibiotics are prescribed for 5-7 days for the treatment of probable neonatal sepsis. This duration of antibiotic therapy is empirical and is not evidence based. The overuse of antibiotics due to above-said concerns might lead to prolonged hospitalization, increased cost of care, unnecessary intravenous catheterization, painful interventions, mother-infant separation, increased colonization by pathogenic organisms and emergence of drug-resistant strains(80).The alarming rise of multidrug and even extensive drug-resistant organisms is a real concern in current neonatal medicine. In South Asia, most isolates of *Klebsiella pneumoniae*, *Escherichia coli* and *Acinetobacter baumannii* are multidrug resistant (2). In view of these problems, there is urgent need to optimize the duration of antibiotic therapy for probable neonatal sepsis to avoid overuse of antibiotics. Therefore, this problem is considered a priority.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: Varies

The important patient-centric desirable effects with biomarker-guided antibiotic therapy are a shorter duration of intravenous antibiotic therapy, and a shorter duration of hospitalization. All three randomized controlled trials (RCT) reported on the duration of antibiotics (84-86).Biomarker-guided therapy was associated with significant reduction in the duration of antibiotic therapy by 0.22 days (95% CI 0.13 days to 0.31 days) as compared to the standard 5-7 days of antibiotic therapy. The quality of evidence was very low due to serious risk of bias, indirectness, and imprecision. Only one RCT reported on the duration of hospitalization (84) . Biomarker-guided therapy did not decrease the duration of hospitalization as compared to the standard course. The desirable effects at the level of the healthcare facility are decrease in the incidence of multidrug-resistant (MDR), extremely drug-resistant (XDR) and pan drug-resistant bacteria (PDR) and decrease in the incidence of fungal sepsis. The panel did not *a priori* plan to assess a decrease in the incidence of MDR, XDR and PDR bacterial and fungal sepsis in healthcare facilities, as these outcomes can only be compared

in a before and after study design, or in large cluster-randomized trials. Nevertheless, during the literature search, none of the studies reported on these outcomes

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: Varies

Critical undesirable effects are mortality (before hospital discharge, by day 28 of life, and by 12 months), death or moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age, and relapse with culture-positive sepsis or meningitis. The important undesirable effect is relapse with culture-positive sepsis or suspected (culture-negative) sepsis, or meningitis. No randomized controlled trials addressed the outcomes of mortality by hospital discharge, mortality by 12 months, and death or moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age. Only one of three included RCTs reported on mortality by 28 days of life (84).Quality of evidence was very low because of serious risk of bias, imprecision, and indirectness. Only one study reported death till 28 days of life, in which one neonate died in standard 5-7 days therapy group (84)**.**The death was attributed to severe birth asphyxia by the authors. Therefore, it is not possible for the review group to consider this outcome for giving recommendation in favour or against the biomarker-guided therapy. The risk estimates include no effect, substantial benefit, and substantial harm. All three RCTs reported on relapse with culture-positive sepsis, probable (culture-negative) sepsis or meningitis (very low quality of evidence because of serious risk of bias, imprecision, and inconsistency), and relapse with culture-positive sepsis or meningitis (low quality of evidence because of serious imprecision and inconsistency (84-86). The relative risk of relapse with either culture-positive, probable sepsis or meningitis was not significant as the 95% confidence interval ranged from 0.59 to 6.47. The relative risk of relapse with culture-positive sepsis or meningitis was also not significant (95% CI ranged from 0.02 to 8.75). The risk estimates were imprecise and include no effect, substantial benefit, and substantial harm. The cost of therapy was not reported by any of the studies. Considering non-availability of evidence for three critically important undesirable outcomes, very less event rates for reported critically important outcome (mortality by 28 days), and low to very low quality of evidence for relapse rates, it is difficult to attribute likelihood of benefit by the biomarker-guided antibiotic therapy as compared to the standard 5-7 days therapy with the available evidence.

Certainty of evidence (what is the overall certainty of the evidence of effects?)

Judgement: Very low

The overall certainty of the evidence of effects is low to very low. Out of five critical outcomes, no evidence was available for 3 critical outcomes (Death by hospital discharge, death by 12 months, and Death or moderate to severe neurodevelopmental impairment at or after 12 months of age), as these outcomes were not reported by any study. Death by 1 month was reported by one study and the single death was attributed to unrelated cause. The low event rate of this outcome along with low quality evidence makes evidence uncertain for the said outcome. The pooled estimate for our critical (relapse with culture-positive sepsis or meningitis within one month) and desirable outcome (relapse with culture-positive sepsis, suspected (culture-negative) sepsis or meningitis within one month), included no effect, substantial benefit, and substantial harm. All 3 RCTs addressed important desirable outcomes (*viz.* duration of antibiotics and duration of hospitalization). For the duration of antibiotics, the 95% confidence interval limits around the pooled estimate showed substantial benefit in favour of biomarker-guided antibiotic therapy. However, the duration of hospitalisation was not significantly different between the two modes of therapy. Overall, the certainty of evidence

was low to very low, and it is possible that the true results might be different from what the research has found.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: No important uncertainty or variability

The guideline panel considers that there is no important uncertainty of variability in how much physicians, parents, policymakers, or public health experts would value the main outcomes, i.e., mortality at various time points and moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and definite relapse of culture proven sepsis or meningitis. There can be no two opinions about the critical importance of avoiding preventable deaths. Moderate to severe neurodevelopmental impairment poses a substantial and lifelong burden on the family, hospitals, the health system, and society. Thus, the panel believes neurodevelopmental impairment is also a universally acknowledged critically important outcome. Relapses with culture proven sepsis necessitate rehospitalisation, painful procedures, re-exposure to antibiotics and the risk of superinfections. Thus, avoiding relapses is important from the point of view of all stakeholders.

Biomarker-guided antibiotic therapy should ideally be non-inferior to a standard course of antibiotics with respect to undesirable effects (such as mortality, relapse, or a neurodevelopmental impairment) and superior with respect to desirable effects (such as duration of antibiotics, duration of hospitalization, and cost of therapy). Although these outcomes would be weighed against each other, more value would be given to mortality, relapse, and neurodevelopmental impairment. In the absence of good quality evidence to show that the biomarker-guided antibiotic therapy is not inferior to the standard course with respect to mortality, relapse-rates, and neurodevelopmental impairment, it would not be possible for the review panel to recommend biomarker-guided therapy solely on the basis of shorter duration of antibiotics.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: Does not favour either the intervention or the comparison

The balance between desirable and undesirable effects does not clearly favour biomarker-guided antibiotic therapy or standard 5-7 days course of antibiotics. Evidence both for the desirable as well as the undesirable effects of a biomarker-guided antibiotic therapy is of low to very low quality mainly because of serious risk of bias, serious imprecision, and indirectness. 95% confidence limits of the absolute effects of biomarker-guided antibiotic therapy includes no effect, substantial benefit, and substantial harm for all the critical outcomes evaluated. Overall, there is a paucity of evidence and literature, with only 3 randomized controlled trials addressing the issue, and several critically important outcomes remaining unaddressed.

Resources required (*How large are the resources required?)*

Judgement: Moderate savings

There is very low-quality evidence that the biomarker-guided antibiotic therapy may result in a shorter duration of antibiotic therapy which might have an impact on duration of hospitalization. None of the trials have reported a cost calculation. Nevertheless, it may be inferred that a shorter duration of antibiotic therapy would result in a modest saving because of lower direct and indirect costs of intravenous infusion of antibiotics and their associated complications. Thus, biomarker-guided antibiotic therapy may reduce costs in the short term.

It is not possible to comment whether a biomarker-guided antibiotic therapy will reduce costs in the long term. With the current state of evidence available from literature, the balance of effects does not favour either biomarker-guided antibiotic therapy or a standard course for the critically important outcomes. Since substantial harm in the form of moderate to severe neurodevelopmental impairment (which would require increased cost of care) and definite relapse (which would require re-hospitalization and re-treatment) cannot be excluded, the possible short-term cost savings may be nullified in the long run.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: No included studies

Only one of the three trials has reported the duration of hospitalization (84). None of the included randomized controlled trials reported a cost calculation. A wide variety of antibiotics and paraphernalia for the administration of antibiotics are used in the treatment of neonatal sepsis. The per day cost of a hospital bed is also extremely variable. Therefore, it is difficult to simulate the expected differences in cost of care

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: Does not favour either the intervention or the comparison

Overall, there is uncertainty about the beneficial effects of biomarker-guided antibiotic therapy for probable neonatal sepsis over standard 5-7 days of antibiotics therapy. Additionally, cost effectiveness was not studied in any of the randomized controlled trials. Furthermore, the quality of evidence for all critically important and important outcomes was low to very low, and the effect includes both substantial benefit and substantial harm. Therefore, the cost effectiveness of the intervention does not favour either the biomarker-guided antibiotic therapy or a standard 5-7 days of antibiotics therapy.

Equity (what would be the impact on health equity?)

Judgement: Don't know

The impact of this intervention on the health equity would be variable. With a few eligible studies and extremely low event rates, it was not possible to check effectiveness separately for various subgroups i.e., probable sepsis, pneumonia, and high-income/low-income settings. With the low to very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm overall as well as in various subgroups.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: Varies

With a low to very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm of biomarker-guided antibiotic therapy. In this context, the acceptability of a biomarker-guided antibiotic therapy would vary between the key stakeholders. Contrastingly, as the standard 5-7 days of antibiotics therapy is empirical and is not evidence based, it might be possible to get changed in future as there is substantial risk of emergence of antibiotic resistance associated with more than desired duration of antibiotic therapy.

Feasibility (is the intervention feasible to implement?)

Judgement: Probably yes

It is feasible to implement the intervention due to a high negative predictive values of biomarkers like C-reactive protein to guide antibiotic therapy (87). The barriers of uncertainty can be overcome by a close follow-up of neonates in the hospital setting for next 2-3 days after stopping antibiotics according to the biomarker-guided therapy. However, due to a low to very low quality of evidence currently available, it is not possible to exclude substantial benefit or substantial harm with either biomarker-guided therapy or standard course of antibiotics

RECOMMENDATION

9. The guidelines group suggests NOT to stop antibiotic therapy based on one or serial negative biomarker report(s) in neonates with uncomplicated@ probable (i.e., culture-negative) neonatal sepsis; these neonates may preferably be treated with the current standard practice of 5-7 days of intravenous antibiotics.

Weak recommendation, Very low certainty of evidence

@ Uncomplicated sepsis defined as any condition that is NOT treated with more than 10-14 days of antibiotics as per current standards of care, e.g., CNS infections, bone and joint infections, deep-seated abscesses

Justification

Overall Justification

The current standard of care i.e., administration of 5-7 days of intravenous antibiotics for the management of probable neonatal sepsis is empirical and is not evidence based. This has become the default intervention as it is being followed for decades. However, the uncertainty of a clear beneficial or harmful effect between a biomarker-guided antibiotic therapy and the standard 5-7 days course is evident after the review. Therefore, in the view of this panel, it would be necessary to demonstrate that a biomarker-guided antibiotic therapy is not inferior to the standard duration with respect to mortality, relapse rates, and neurodevelopmental impairment to shorten the duration of antibiotics. Considering that the evidence is inconclusive and there is only weak evidence in favour of biomarker-guided antibiotic therapy, the panel decided to make a weak recommendation against the intervention.

Detailed justification

Desirable Effects

The desirable effect is a shorter duration of antibiotic therapy and duration of hospitalization. However, the quality of evidence for this outcome was very low because of serious risk of bias, imprecision, and indirectness.

Undesirable Effects

The quality of evidence for critical outcomes such as mortality, moderate to severe neurodevelopmental impairment, and relapse of definite culture proven relapse of sepsis/meningitis was low because of serious imprecision and indirectness. The quality of evidence for important outcomes such as relapse of culture-proven, or probable relapse of sepsis/meningitis was very low because of serious risk of bias, imprecision, and indirectness.

Certainty of evidence
Evidence was of low to very low quality

Subgroup considerations

No subgroup analyses were performed

Implementation considerations

Based on the current evidence, the panel gives a weak recommendation against the biomarker-guided antibiotic therapy for probable neonatal sepsis

Monitoring and evaluation

Since the panel gives a weak recommendation against the intervention (biomarker-guided antibiotic therapy) and advises continuation of a standard (5-7 days) course of antibiotics for probable neonatal sepsis, there is no extra monitoring or evaluation required over and above the current clinical practice. However, if any unit deviates from the current recommendations, and follows biomarker-guided antibiotic therapy, the safety of the neonates can be increased by following means: close follow-up of neonates in hospital setting for the next 2-3 days after completion of antibiotics, and utilization of negative predictive values of acute phase reactants by documenting negative biomarkers more than once

Research priorities

Given the paucity of evidence, the panel recommends undertaking noninferiority, randomized controlled trial to compare biomarker-guided antibiotic therapy versus standard 5–7-day course of antibiotics in uncomplicated, probable (i.e., culture-negative) neonatal sepsis

***Practice Question 10*: Among newborn infants with definite or probable meningitis, is a shorter course of antibiotics (typically 14 days) non-inferior to a standard course of antibiotics (typically 21 days)?**

Pico question

P= Neonates with definite or probable uncomplicated meningitis
I= short course of intravenous antibiotics (typically 14 days)
C= standard course of intravenous antibiotics (typically 21 days)
O= Mortality before discharge from hospital; Mortality by day 28 of life; Mortality by 12 months of corrected age; Relapse with culture-positive sepsis or meningitis; Relapse with culture-negative (probable) sepsis or meningitis; Duration of antibiotic therapy; Moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness); Death or moderate or severe neurodevelopmental impairment at or after 12 months of age; Seizures needing more than one anticonvulsant during follow-up (epilepsy)

Summary of evidence

Table 10 depicts the summary of evidence.

Table 10: Summary of findings

Patient or population: treatment of definite or probable uncomplicated neonatal meningitis
Setting: all settings
Intervention: a short course of intravenous antibiotics (typically 14 days)
Comparison: a standard course of intravenous antibiotics (typically 21 days)

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with a standard course of intravenous antibiotics (typically 21 days)	**Risk with a short course of intravenous antibiotics (typically 14 days)**				
Mortality before discharge from hospital	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	
Mortality by day 28 of life	57 per 1,000	**29 per 1,000** (3 to 301)	**RR 0.50** (0.05 to 5.27)	70 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d,e]	The evidence is very uncertain about the effect of a short course of intravenous antibiotics (typically 14 days) on mortality by day 28 of life.
Mortality by 12 months of corrected age	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	
Relapse with culture-positive sepsis or meningitis	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	70 (1 RCT)	⨁⨁◯◯ LOW [b,c,e,f,g]	The evidence is very uncertain about the effect of a short course of intravenous antibiotics (typically 14 days) on relapse with culture-positive sepsis or meningitis.
Relapse with culture-negative (probable) sepsis or meningitis	86 per 1,000	**0 per 1,000** (0 to 185)	**RR 0.00** (0.00 to 2.16) [h]	70 (1 RCT)	⨁◯◯◯ VERY LOW [b,c,e,i,j]	The evidence is very uncertain about the effect of a short course of intravenous antibiotics (typically 14 days) on relapse with culture-negative (probable) sepsis or meningitis.
Duration of antibiotic therapy	The mean duration of antibiotic	**0** (0 to 0)	-	(0 studies)	-	

	therapy was **0**				
Moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant, cerebral palsy, cognitive disability, blindness or deafness)	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-
Death or moderate or severe neurodevelopmental impairment at or after 12 months of age	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-
Seizures needing more than one anticonvulsant during follow-up (epilepsy)	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

Explanations
a. The risk of bias was assessed to be "not serious" because it was particularly difficult to mask the nature of the intervention and the outcome was all-cause mortality which does not have measurement bias
b. Inconsistency cannot be judged because there was only one study
c. The study compared a 10 day course versus a 14 days course of antibiotic treatment for neonatal meningitis, whereas the GRADE question was related to a comparison of a short course (typically 14 days) versus a standard course (typically 21 days) of antibiotics. The diagnosis of neonatal meningitis in the study was based on presence of only >32 cells per microlitre in the cerebro-spinal fluid examination of a sick neonate with either of an abnormal blood leukocyte count, raised immature to total ratio, elevated micro-erythrocyte sedimentation rate, and raised C-reactive protein. Cerebro-spinal fluid culture, glucose or protein were not considered for diagnosis.
d. The 95% confidence interval limits were 0.05 to 5.27
e. Publication bias cannot be judged because there was only one study
f. The risk of bias was assessed to be "not serious" because it was particularly difficult to mask the nature of the intervention and the outcome was culture-positive sepsis or meningitis which has relatively less measurement bias (compared to culture-negative sepsis or meningitis)
g. Not applicable as there were no events in either group
h. The figures were entered manually because the automatic calculation was showing "not estimable"
i. The sole RCT was judged to have a high risk of performance bias due to lack of blinding, because culture-negative sepsis is a relatively subjective outcome.
j. 95% confidence interval of RR ranged from 0 to 2.16

Summary of judgements

Problem (is the problem a priority?)

Judgement: Yes

Neonatal sepsis is an important cause of morbidity and mortality. Globally, neonatal sepsis accounts for 8% of all neonatal deaths in the 1st week of life and 37% of all deaths from the 2nd to 4th weeks of life (1). In hospital settings, the incidence of culture proven neonatal sepsis is 16 per 1000 live births in India (2).One large study from a rural community in India reported 4 cases of culture proven neonatal sepsis per 1000 live births (3). Population-based studies from India report highly variable incidences of clinically suspected sepsis- ranging from 4.6 to 170 per 1000 live births (4).Given the high incidence of sepsis, the use of antibiotics in the neonatal period is very high all over the world, particularly so in India.

The overuse and prolonged use of antibiotics, even in situations where it is not necessary, has resulted in an alarming problem of multidrug resistant neonatal sepsis. In South Asia, most isolates of Klebsiella pneumoniae, Escherichia coli and Acinetobacter baumannii are multidrug resistant (2).The reliance on newer generations of antibiotics has also increased the cost of care and the incidence of serious adverse events. In view of these problems, it is important to optimize the duration of antibiotic therapy, so that longer courses of antibiotics are not administered where shorter courses would do the job. If shorter courses of antibiotics are found to be as efficacious as standard courses, without any increased risk of relapses, complications, or mortality, then shorter courses could safely replace longer courses.

Shorter courses of antibiotics would be expected to cause less serious adverse events, require shorter hospitalization, incur less cost, and decrease the risk of secondary bacterial infections. When scaled up to the level of the community, the benefits, if any, of shorter courses of antibiotics would be enormous, resulting in many more hospital beds being freed up, and less financial burden on the public health system.

Meningitis is one of the common and dreaded complications of neonatal sepsis. Meningitis complicates anywhere between 5 to 15% of all cases of neonatal sepsis (88-90). Inadequately treated meningitis may result in long-term consequences such as neurodevelopmental impairment, cerebral palsy, mental retardation, epilepsy, deafness, and hydrocephalus. Although most textbooks recommend a 21-day duration of antibody therapy and this is commonly followed in clinical practice, this duration is not based on evidence. In a survey conducted by the panellists, the comparison of a short course of antibiotics (typically 14 days) versus a standard course of antibiotics (typically 21 days) for uncomplicated Meningitis among neonates was rated to be extremely important.

In view of all the above facts, this problem is considered a priority.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: varies

The important desirable effects with short course of antibiotics at the level of the individual patient are shorter duration of antibiotic therapy and a shorter duration of hospitalisation; and at the level of the healthcare facility are decrease in the incidence of multidrug-resistant (MDR), extremely drug-resistant (XDR) and pan drug-resistant bacteria (PDR) and decrease in the incidence of fungal sepsis.

There was no study that reported on duration of antibiotic therapy or duration of hospitalisation. Although the sole randomised controlled trial did not report on the actual duration of antibiotic therapy, it can be surmised that subjects receiving a short course antibiotics arm would have received fewer days of antibiotics compared to those receiving a standard course (91).

Based on a survey, the panel did not *a priori* plan to assess the decrease in the incidence of MDR, XDR and PDR bacterial and fungal sepsis in the healthcare facility, as these outcomes can only be compared in a before and after study design, or in large cluster-randomized trials or after short course of antibiotics is implemented in the unit as a policy for all infants. Nevertheless, during the literature search, none of the studies reported on these outcomes.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: varies

Critically important undesirable effects are mortality (before hospital discharge, by day 28 of life and by 12 months of post-term corrected age), moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and death or moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age, relapse with culture-positive sepsis or meningitis, and seizures requiring more than one anticonvulsant drug during follow-up. The important effect is relapse with suspected (culture-negative) sepsis or meningitis.

There were no randomized controlled trials addressing the outcomes of death before hospital discharge, death by 12 months of post-term corrected age, moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age, death or moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and duration of antibiotic therapy and epilepsy on follow-up.

1 randomized controlled trial reported on mortality by day 28 of life. Quality of evidence was very low because of very serious indirectness and serious imprecision. The absolute effect on mortality by day 28 of life ranged from 54 fewer deaths to 244 more deaths per 1000 subjects. The risk estimates are imprecise and include no effect, substantial benefit, and substantial harm.

1 randomized controlled trial reported on relapse with culture-positive sepsis or meningitis, and relapse with suspected (culture-negative) sepsis or meningitis. Quality of evidence was very low both for relapse with culture-positive sepsis meningitis and for culture negative sepsis meningitis. There was very serious indirectness for relapse with culture-positive sepsis or meningitis. There was serious risk of bias, very serious indirectness, and serious imprecision for relapse with culture-negative sepsis or meningitis. The effects on relapse with culture-positive sepsis or meningitis could not be calculated as there were no events. The absolute effect on relapse with culture-negative sepsis meningitis ranged from 86 fewer relapses to 31 more relapses per 1000 subjects.

Certainty of evidence (what is the overall certainty of the evidence of effects?)

Judgement: very low

The overall certainty of the evidence of effects is very low. There is no evidence available for most of the critical outcomes, barring 28-day mortality and relapse with culture-positive sepsis meningitis. No randomized controlled trial addressed desirable outcomes. The sole RCT addressed two undesirable critical outcomes. For both the critical undesirable outcomes, the risk estimates were imprecise and the 95% confidence interval limits around the pooled estimate included no effect, and substantial benefit and substantial harm.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: no important uncertainty or variability

A shorter course of antibiotics should ideally be non-inferior to a standard course of antibiotics with respect to undesirable effects such as mortality, relapse, or a

neurodevelopmental impairment and superior with respect to duration of antibiotics, duration of hospitalization, cost, incidence of adverse effects, discomfort, and pain. Although these outcomes would be weighed against each other, more value would be given to mortality, relapse, and neurodevelopmental impairment. In the absence of good quality evidence to show that shorter courses are not inferior to standard courses with respect to mortality, relapse, and neurodevelopmental impairment, it would not be possible to recommend shorter courses solely based on shorter duration of antibiotics, shorter hospitalization and so on.

The guideline panel considers that there is no important uncertainty of variability in how much physicians, parents, policymakers, or public health experts would value the main outcomes, i.e., mortality at various time points and moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and definite relapse of culture proven sepsis or meningitis. There can be no 2 opinions about the critical importance of avoiding preventable deaths. Moderate to severe neurodevelopmental impairment poses a substantial and lifelong burden on the family, hospitals, the health system, and society. Thus, the panel believes neurodevelopmental impairment is also a universally acknowledged critically important outcome. Relapses with culture proven sepsis necessitate rehospitalisation, painful procedures, re-exposure to antibiotics and the risk of superinfections. Thus, avoiding relapses is important from the point of view of all stakeholders.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: does not favour either the intervention or the comparison

The balance between desirable and undesirable effects does not favour either the intervention of the comparison. Evidence for 28-day mortality benefits of a short course of antibiotics is of very low quality because of very serious indirectness and serious imprecision. 95% confidence limits of the absolute effects of a short course of antibiotics includes no effect, substantial benefit, and substantial harm for 28-day mortality. Overall, there is a paucity of evidence and literature, with only 1 small randomized controlled trial addressing the issue, and several critically important outcomes remaining unaddressed.

Resources required (*How large are the resources required?)*

Judgement: don't know

None of the trials have reported a cost calculation, duration of hospitalisation or duration of antibiotics. Although none of the trials had reported on the actual duration of antibiotic therapy, it is almost self-evident that shorter duration of antibiotics would cost less than standard duration of antibiotics. Thus, shorter duration of antibiotics may reduce costs in the short term.

It is not possible to comment whether short duration of antibiotics will reduce costs in the long term. With the current state of evidence available from literature, the balance of effects does not favour either a short course of antibiotics or a standard course for the critically important outcomes. Since substantial harm in the form of moderate to severe neurodevelopmental impairment (which would require increased cost of care) and definite relapse (which would require re-hospitalization and re-treatment) and seizures (requiring multiple antiepileptic drugs) cannot be excluded, the possible short-term cost savings may be nullified in the long run.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: no included studies

Shorter duration of antibiotics and lesser days of hospitalization are expected to decrease costs. However, none of the included randomized controlled trials reported a cost calculation. A wide variety of antibiotics and paraphernalia for the administration of antibiotics are used in the treatment of neonatal sepsis. The per day cost of a hospital bed it is also extremely variable, depending upon the level of care. Therefore, it is difficult to simulate the expected difference in cost of care.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: no included studies

Cost effectiveness was not studied in any of the randomized controlled trials. The cost effectiveness of the intervention does not favour either the intervention or the comparison because the quality of evidence for all critically important and important outcomes is very low, and the effect includes both substantial benefit and substantial harm. The issue of cost effectiveness would arise only if it were possible to conclude that the intervention provides at least some benefit for critical outcomes.

Equity (what would be the impact on health equity?)

Judgement: varies

The impact on health equity would be variable. With the very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm. If the truth is that short course of antibiotics reduces the duration of antibiotic therapy and duration of hospitalization without substantial increase in mortality, relapse or long-term neurodevelopmental impairment, the intervention would increase health equity, as antibiotic therapy for neonatal sepsis would be more affordable for everybody. However, if the truth is that short course of antibiotics increases mortality, relapse or long-term neurodevelopmental impairment, the intervention would reduce health equity, as substantially more cost and resources would be required to manage episodes of relapse and managing neurodevelopmental impairment.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: varies

With the very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm. In this context, the acceptability of short course of antibiotics would vary between the key stakeholders.

Feasibility (is the intervention feasible to implement?)

Judgement: yes

In principle, the intervention (short course of antibiotics) is very feasible to implement because it requires less resources. However, the issue of feasibility does not arise at present. With the very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm with either the short course or standard course of antibiotics.

RECOMMENDATION

10. The guidelines group suggests NOT to use a short course of intravenous antibiotics (typically 14 days or less) in neonates with definite or probable uncomplicated[$] neonatal meningitis; these neonates may preferably treated with the standard course of antibiotics (typically 21 days).

Weak recommendation, Very low certainty of evidence

[$] Uncomplicated meningitis defined as CNS infections that DOES NOT require more than 21 days of antibiotics as per current standards of care, e.g. ventriculitis, cerebral abscess, subdural empyema

Justification

Overall justification

Although there is no prescribed standard of care currently, most units tend to prescribe antibiotics for 21 days in uncomplicated neonatal meningitis, and over the years this has become default duration, despite the lack of evidence to back it. Therefore, in the view of this panel, to shorten the duration of antibiotics, it would be necessary to demonstrate that shorter duration of antibiotics is not inferior to the standard duration with respect to mortality, relapse rates, neurodevelopmental impairment, and epilepsy. Since the evidence in literature is inconclusive about these critical outcomes, any kind of recommendation in favor of the intervention (short course) it is not possible. Considering that the evidence is inconclusive, the panel decided to make a weak recommendation against the intervention.

Detailed justification

Desirable Effects

There is no evidence in literature regarding duration of hospitalization or duration of antibiotics.

Undesirable Effects

The quality of evidence for critical outcomes such as mortality, and relapse with culture-positive sepsis meningitis was very low to low because of very serious indirectness and serious imprecision.

Certainty of evidence

Evidence was a very low to low quality

Subgroup considerations

No subgroup analyses were performed

Implementation considerations

The panel suggests to not administer a short course of antibiotics for suspected or proven neonatal bacterial meningitis. If, at a future date, evidence emerges that short course antibiotic therapy is associated with substantially greater benefit than harm, then implementation of short course antibiotic therapy is unlikely to require any special prerequisites, training, infrastructure, or expenditure.

Monitoring and evaluation

Since the panel suggests against administering short-course antibiotics, there is no extra monitoring or evaluation that needs to be done, over and above what is currently being done.

Research priorities

Given the paucity of evidence, the panel recommends that large multi-centric non-inferiority open-label, randomized controlled trials must be conducted to compare shorter courses of antibiotics versus standard courses of antibiotics in uncomplicated, neonatal bacterial meningitis.

***Practice Question 11*: Among Newborn infants with complicated meningitis (ventriculitis, abscess), is a shorter course of antibiotics (typically <= 4 weeks) non-inferior to a standard course of antibiotics (typically 6 weeks)?**

Pico question

P= Newborn infants with complicated meningitis (ventriculitis, brain abscess)
I= Shorter course of antibiotics (<4 weeks)
C= Longer course of antibiotics (6 weeks)
O= Mortality during hospital stay; Mortality within day 28 of life; Mortality by one year of corrected age; Moderate or severe neurodevelopmental impairment at or after 12 months of age (Either of seizures needing more than one anticonvulsant on follow up or cerebral palsy or cognitive disability or blindness or deafness); Death or moderate or severe neurodevelopmental impairment at or after 12 months of age (either of seizures needing more than one anticonvulsant on follow-up or cerebral palsy or cognitive disability or blindness or deafness); Seizures needing more than 1 anticonvulsant during follow-up (epilepsy); Duration of antibiotic therapy; Duration of hospital stay; Hydrocephalus requiring surgical intervention;

Summary of evidence

No eligible studies could be found.

Summary of judgements

Problem (is the problem a priority?)

Judgement: Yes

Bacterial meningitis is more common in neonatal period than any other time of life and is a devastating clinical condition with significant morbidity and mortality. The incidence of neonatal meningitis ranges from 0.21 to 0.5 per 1,000 newborns in developed countries and as high as 6.1 per 1,000 live births in developing countries (13, 47). Mortality due to neonatal meningitis is 40-58% in developing countries as compared to 10% in developed countries (92). The complications of meningitis due to inadequate treatment or delayed diagnosis or severe infection include ventriculitis, brain abscess, cerebral oedema, raised intracranial pressure, subdural empyema, hydrocephalus, infarct and sinus venous thrombosis. Survivors of meningitis have serious disabilities like developmental delay, hearing and visual defects. Studies show that 23% (19- 26%) neonates at follow-up have moderate to severe disability and 12% (5-19%) have severe disability (48).

There is an alarming increase in the incidence of neonatal infection with multidrug drug resistant strains of Acinetobacter, Klebsiella and E coli all over the world especially in Asian countries (2). Use of prolonged antibiotic therapy in conditions where short courses would suffice will result in increased antibiotic resistance. Hence if shorter course of antibiotics can be proven to be as efficacious as longer courses in decreasing mortality, relapses, neurodevelopmental impairment and sequelae like hydrocephalus, they can be safely used in clinical practice. In addition, shorter courses would provide benefits by decreasing duration of treatment and cost of care if clinical outcomes are as efficacious as longer courses.

The conventional treatment options for complicated meningitis include prolonged antibiotic therapy (ranging from 3-12 weeks) both intravenous and intraventricular and surgical interventions like ventriculo-peritoneal shunt, external ventricular drainage, drainage/excision of abscess cavity. Though there are guidelines regarding the treatment of healthcare associated meningitis/ventriculitis (93), there are no recommendations for optimal duration of antibiotics in community acquired complicated meningitis.

In a survey conducted by the panellists, the comparison of a short course of antibiotics versus a standard course of antibiotics for complicated meningitis among neonates was rated to be extremely important. Considering the above facts, the problem is a priority.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: Varies

The important desirable effects with short course of antibiotics are shorter duration of hospitalization and antibiotic therapy, decreased cost of care, decrease in the incidence of multidrug-resistant (MDR), extremely drug-resistant (XDR) and pan drug-resistant bacteria (PDR), and decrease in the incidence of fungal sepsis.

Since there were no eligible analytical studies, there is no evidence regarding the same

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: Varies

Critically important undesirable effects of short course of antibiotics are mortality (before hospital discharge, by day 28 of life and by 12 months of post-term corrected age), moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and death or moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age, relapse with culture-positive sepsis or meningitis, hydrocephalus requiring surgical intervention. The important effect is relapse with suspected (culture-negative) sepsis or meningitis.

During literature search no eligible analytical studies were identified.

Certainty of evidence (what is the overall certainty of the evidence of effects?)

Judgement: No included studies

Certainty of evidence can't be ascertained as there were no eligible studies to be included.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: No important uncertainty or variability

The guideline panel considers that there is no important uncertainty of variability in how much people value the main outcomes, i.e. mortality at various time points and moderate to severe neurodevelopmental impairment by 12 months of corrected age, definite relapse of culture proven sepsis or meningitis and hydrocephalus requiring surgical intervention. Neurodevelopmental impairment can have a significant impact on health, economic and

social aspects and decrease the quality of life significantly (78, 94). Relapses with culture proven sepsis necessitate rehospitalisation, painful procedures, re-exposure to antibiotics and the risk of superinfections. Thus, avoiding relapses is important from the point of view of all stakeholders. A shorter course of antibiotics should ideally be non-inferior to a standard course of antibiotics with respect to undesirable effects such as mortality, relapse or a neurodevelopmental impairment and superior with respect to duration of antibiotics, duration of hospitalization, cost, incidence of adverse effects, discomfort and pain. In the absence of good quality evidence to show that shorter courses are not inferior to standard courses with respect to mortality, relapse and neurodevelopmental impairment, it would not be possible to recommend shorter courses solely on the basis of shorter duration of antibiotics, shorter hospitalization and so on.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: Varies

Since there were no eligible studies for inclusion the balance between desirable and undesirable effects cannot be commented upon.

Resources required (*How large are the resources required?)*

Judgement: Varies

Though logically shorter duration of antibiotics will decrease the duration of antibiotic use, hospitalisation and hence cost of care, there is lack of evidence to comment whether short duration of antibiotics will reduce costs in the long term. Since substantial harm in the form of moderate to severe neurodevelopmental impairment (which would require increased cost of care) and definite relapse (which would require re-hospitalization and re-treatment) cannot be excluded, the possible short-term cost savings may be nullified in the long run.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: No included studies

Certainty of evidence of required resources cannot be ascertained as there were no eligible studies for inclusion.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: No included studies

Short of evidence to recommend short course antibiotics, it is not possible to comment whether cost effectiveness would favour short course or standard course of antibiotics.

Equity (what would be the impact on health equity?)

Judgement: Varies

In the absence of evidence, the impact on health equity would be variable. Short course of antibiotics may reduce the duration of antibiotic therapy and duration of hospitalization without substantial increase in mortality, relapse or long-term neurodevelopmental impairment or complications like hydrocephalus in which case the intervention would increase health equity, as antibiotic therapy for neonatal complicated meningitis would be more affordable for everybody. However, if short course of antibiotics increases mortality, relapse or long-term neurodevelopmental impairment, the intervention would reduce health equity, as

substantially more cost and resources would be required to manage episodes of relapse and managing neurodevelopmental impairment.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: Yes

Since evidence is currently unavailable, it is not possible to exclude substantial benefit or substantial harm. In this context, the acceptability of short courses of antibiotics would vary between the key stakeholders.

Feasibility (is the intervention feasible to implement?)

Judgement: Yes

In principle, the intervention (short course of antibiotics) is very feasible to implement because it requires less resources. However, with the absence of evidence for the same, the issue of feasibility does not arise at present.

RECOMMENDATION

11. The guidelines group suggests NOT to use a shorter course of antibiotics (<4 weeks) in newborn infants with complicated meningitis (ventriculitis, brain abscess); these neonates may preferably be managed with the standard longer course of antibiotics (4-6 weeks).

Weak recommendation, Not graded (Expert consensus)

Justification

Although there are no guidelines on optimal duration of antibiotics for complicated meningitis, the standard of care currently in most units tends to be 4-6 weeks of antibiotics with surgical interventions (VP shunt, EVD, drainage of intracranial abscess) when needed. Therefore, in the view of this panel, to shorten the duration of antibiotics (<4 weeks), it would be necessary to demonstrate that shorter duration of antibiotics is not inferior to the standard duration with respect to mortality, relapse rates and neurodevelopmental impairment. Since there is no current evidence in literature about these critical outcomes, any kind of recommendation in favour of the intervention (short course) is not possible. Therefore, the panel decided on a weak recommendation against the intervention.

Overall, the panel's recommendation is to continue with the current default practice of 4-6 weeks of intravenous antibiotics for complicated neonatal meningitis with surgical intervention decided on case-to-case basis, until more robust evidence is available.

Subgroup considerations

No subgroup analysis done

Implementation considerations

Currently the panel does not recommend a short course of antibiotics (<4 weeks) for complicated neonatal meningitis. If, at a future date, evidence emerges that short course antibiotic therapy is associated with substantially greater benefit than harm, then implementation of short course antibiotic therapy is unlikely to require any special prerequisites, training or infrastructure. Since in most of the cases of complicated meningitis, neuroimaging (USG, CT, MRI) may be required to assess treatment response and some investigators in adult studies (12) (9) have used CRP to decrease antibiotic duration in surgically treated brain abscess patients, if at all short course of antibiotics are implemented in future then additional neuroimaging and CRP before stopping antibiotics may be required.

Monitoring and evaluation

Since the panel gives a conditional recommendation against the intervention (short-course antibiotics) and advises continuation of the standard (4-6 weeks) course of antibiotics, there is no extra monitoring or evaluation that needs to be done, over and above what is currently being done.

Research priorities

In view of lack of evidence, the panel recommends that large multi-centric non-inferiority open-label, randomized controlled trials must be conducted to compare shorter courses of antibiotics versus standard courses of antibiotics in complicated neonatal meningitis.

***Practice Question 12*: In newborn infants with uncomplicated UTI is a shorter course of antibiotics (typically ≤ 10 days) non-inferior to a standard course of antibiotics (typically 14 days)?**

Pico question

P= Newborn infants with uncomplicated Urinary tract infection (UTI)
I= shorter course of antibiotics (typically ≤ 10 days)
C= a standard course of antibiotics (typically 14 days)
O =Mortality during hospital stay; mortality within day 28 of life; mortality by 12 months of corrected age; relapse with culture-positive sepsis or meningitis or urinary tract infection; relapse with culture-negative sepsis or meningitis or urinary tract infection; chronic renal failure; duration of antibiotic therapy; duration of hospital stay; serious adverse drug reactions; and cost of care

Summary of evidence

Table 11 depicts the summary of evidence.

Table 11: Summary of findings

Patient or population: newborn infants with uncomplicated UTI
Setting: All settings
Intervention: shorter course of antibiotics (typically ≤ 10 days)
Comparison: a standard course of antibiotics (typically 14 days)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with a standard course of antibiotics (typically 14 days)	Risk with shorter course of antibiotics (typically ≤ 10 days)				
Mortality during hospital stay	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	
Mortality within day 28 of life	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	
Mortality by 12 months of corrected age	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	
Relapse with culture-positive sepsis or meningitis or urinary tract infection	23 per 1,000	16 per 1,000 (13 to 21)	RR 0.72 (0.56 to 0.93)	12448 (2 observational studies)	⨁◯◯◯ VERY LOW [a,b,c,d]	
Relapse with culture-negative sepsis or meningitis or urinary tract infection	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	
Chronic renal failure	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-	
Duration of antibiotic therapy	The mean duration of antibiotic therapy was 0	0 (0 to 0)	-	(0 studies)	-	

Duration of hospital stay	The mean duration of hospital stay was 10.8 days	MD 6 days fewer (4 fewer to 8.8 fewer)	-	115 (1 observational study)	⊕◯◯◯ VERY LOW [a,b,d]
Serious adverse drug reactions	0 per 1,000	0 per 1,000 (0 to 0)	not estimable	(0 studies)	-
Cost of care	The mean cost of care was 0	0 (0 to 0)	-	(0 studies)	-

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; RR: Risk ratio; MD: Mean difference

Explanations
a. Retrospective Cohort Studies
b. Serious risk of bias on ROBINS-I Tool
c. Brady 2010 study enrolled infants <6 months. Desai 2019 study enrolled infants ≤60 days
d. Negative studies not likely to be published

Summary of judgements

Problem (is the problem a priority?)

Judgement: Yes

In newborn infants, urinary tract infection (UTI) is defined as positive urine culture obtained by suprapubic aspiration or a catheterized specimen with a colony count > 1,000 colonies per ml in centrifuged urine. Neonates, especially premature neonates, are likely at higher risk for UTI and urosepsis based on multiple factors. Increased susceptibility, prolonged hospitalization, multiple interventions, including intravascular catheters, and exposure to multiple antibiotic courses may contribute to a prevalence rate as high as 20% in premature and low birth weight infants (95).

UTI is the most common bacterial infection in febrile neonates (96) .The true incidence of UTI in newborn infants is very difficult to find. The estimated prevalence of UTI in infants less than 2 to 3 months ranges from 4.6 to 13.6% (97-99).The pooled prevalence rates of febrile UTIs in females aged 0-3 months was 7.5%, and among febrile male infants less than 3 months of age, 2.4% (CI: 1.4-3.5) of circumcised males and 20.1% (CI: 16.8-23.4) of uncircumcised males had a UTI (98) .

The most common organisms causing UTI in neonates are E. Coli seen in 40-72% followed by Enterococcus (10-16%) and Klebsiella (7-40%) (99-101). The gold standard for diagnosis of UTI is positive urine culture. Urine culture is typically obtained through 3 different methods in infants: urinary catheterization, suprapubic aspiration, or sterile bag collection. The sterile bag method is associated with a high rate of contamination as compared with other methods and hence best avoided. Although definitions of UTI vary, some investigators have defined a positive urine culture as the growth of a known bacterial pathogen from a catheterized specimen at a level of ≥50,000 colony-forming units (CFU)/mL or ≥10,000 CFU/mL in association with a positive dipstick test or urinalysis (95-97, 100, 101).

Non-invasive cultures typically are regarded as positive if they grow ≥ 100,000 CFU/mL while the growth of any bacteria is regarded as significant if collected with a SPA. Recommendations for catheterized samples vary between 1,000 and 10,000 CFU/mL (102, 103) . CFU less than 50,000 per ml may be classified as asymptomatic Bacteriuria.

UTIs can be clinically grouped into asymptomatic Bacteriuria, cystitis, and acute Pyelonephritis (104-106) .

• Asymptomatic Bacteriuria is the presence of Bacteriuria without clinical signs and symptoms.

• Cystitis is a UTI limited to the urethra and bladder and is seen most commonly in girls over two years of age.

• Acute Pyelonephritis refers to infection of the kidneys and is the most severe form of UTI in children.

The precise localization in newborn babies is unlikely and the majority of the time they have cystitis and Pyelonephritis is rare.

The neonates with UTI are managed by using intravenous antibiotics. The duration of treatment in neonates with UTI is controversial (107-112).The route of administration of antibiotics and duration of antibiotics is usually decided by the severity of illness and the majority of the times clinicians administer the antibiotics (route- either completely parenteral or parenteral followed by enteral) for 7-14 days, though the optimal duration of antibiotics is not known. There are wide variations in recommendations from professional organizations such as AAP, NICE, EAU/ESPU, Canadian Pediatric Society (CPS), and other (103, 113-115) . The American Academy of Pediatrics clinical practice guideline for the management of UTIs includes infants between 2 and 24 months of age (duration 7-14 days) but does not provide guidance for infants <2 months (113).This has resulted in significant variability in the duration of parenteral therapy in young infants with UTIs, although the factors that drive this variation are less clear (109).

The short course of antibiotics may be associated with treatment failure and a longer course may result in prolonged exposure of antibiotics to the neonate, which may result in antimicrobial resistance and adverse effects of drugs. Since the duration of optimal antibiotics is not known, we decided to find the optimal duration and if a short course versus a long course is appropriate for UTI in neonates.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: Varies

The important desirable effects with a short course of antibiotics at the level of the individual patient are a shorter duration of hospitalization and antibiotic therapy; and at the level of the healthcare facility is a decrease in the incidence of multidrug-resistant (MDR), extremely drug-resistant (XDR) and pan drug-resistant bacteria (PDR), and decrease in the incidence of fungal sepsis.

We could not find any systematic review or RCTs in the newborn infants that addressed this question. Out of the two included observational studies (116, 117); one study (117) reported on the duration of hospitalization. The quality of evidence was low because of the serious risk of bias. The absolute effect on the duration of hospitalization: MD 6 fewer days (range from 4 to 8.8 fewer days) of hospitalization with a short course of antibiotics. Although none of the two observational studies have reported on the actual duration of antibiotic therapy (parenteral plus oral), it can be surmised that subjects receiving a short course of antibiotics would have fewer days of antibiotics compared to those receiving a standard course.

The panel did not *a priori* plan to assess the decrease in the incidence of MDR, XDR, and PDR bacterial and fungal sepsis in the healthcare facility, as these outcomes can only be compared in a before and after study design, or large cluster-randomized trials or after a short course of antibiotics is implemented in the unit as a policy for all infants. Nevertheless, during the literature search, none of the studies reported on these outcomes.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: Varies

Critically important undesirable effects are mortality (before hospital discharge, by day 28 of life, and by 12 months of post-term corrected age), relapse with culture-positive sepsis or meningitis or urinary tract infection, relapse with culture-negative sepsis or meningitis or urinary tract infection, and chronic renal failure.

We could not find any systematic review or RCTs in the newborn that addressed this question. Out of the two included observational studies (116, 117) none reported on the outcomes of mortality, relapse with culture-negative sepsis or meningitis or urinary tract infection, and chronic renal failure.

Both observational studies reported on the outcome of relapse with culture-positive urinary tract infection (116, 117) .

The quality of evidence was very low because of the serious risk of bias. The rate of relapse of culture-positive UTI was 1.6% in the short-duration group versus 2.3% in the long-duration group (p=0.01). The absolute effect on relapse with culture-positive UTI ranged from 2 to 10 fewer UTI in favour of short course. The risk estimates although are in favour of a short course, it cannot be completely relied on because of the retrospective cohort nature of both included studies.

Certainty of evidence (what is the overall certainty of the evidence of effects?)

Judgement: Very Low

The overall certainty of the evidence of effects is very low. Although there are systematic reviews about the treatment of urinary tract infection in children, none of them are pertinent to newborn infants (118-123) .There are no RCTs or prospective cohort studies in newborn infants on this topic. We could only find two observational retrospective cohort studies on the impact of short versus long duration of parenteral antibiotic treatment in UTI in newborn infants (116, 117). These studies reported on only two of the nine outcomes of interest: the rate of relapse of culture-positive UTI (both studies) and duration of hospitalization (one study). Also, these studies do not elaborate on the total duration of antibiotics (parenteral plus post-discharge oral), wherein, post-discharge information regarding the duration of oral antibiotics is not provided. Moreover, post-hoc statistical adjustments for baseline covariates in retrospective cohort studies would always have limitations.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: No important uncertainty or variability

A shorter course of antibiotics should ideally be non-inferior to a standard course of antibiotics concerning undesirable effects such as mortality or relapse and superior for the duration of antibiotics, duration of hospitalization, cost, the incidence of adverse effects, discomfort, and pain. Although these outcomes would be weighed against each other, more value would be given to mortality and relapse. In the absence of good quality evidence to show that shorter courses are not inferior to standard courses for mortality, relapse, and neurodevelopmental impairment, it would not be possible to recommend shorter courses solely based on the shorter duration of antibiotics, shorter hospitalization, and so on.

The guideline panel considers that there is no important uncertainty or variability in how much physicians, parents, policymakers, or public health experts would value the main outcomes, i.e. mortality at various time points and definite relapse of culture-proven UTI. There cannot be two opinions about the critical importance of avoiding preventable deaths. Relapses with culture-proven UTI and sepsis necessitate re-hospitalization, painful procedures,

re-exposure to antibiotics, and the risk of superinfections. Thus, avoiding relapses is important from the point of view of all stakeholders.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: Does not favour either the intervention or the comparison

The overall certainty of the evidence of effects is very low. The balance between desirable and undesirable effects does not favour either the intervention or the comparison.

Evidence both for the desirable as well as the undesirable effects of a short course of antibiotics is of very low quality because the evidence is coming from retrospective cohort studies with a serious risk of bias. Overall, there is a paucity of evidence and literature, with only two retrospective cohort studies on the issue, and seven of the nine critical or important outcomes remaining unaddressed.

Resources required (*How large are the resources required?)*

Judgement: Moderate savings

There is low-quality evidence that a shorter course of antibiotics may result in a shorter duration of hospitalization. Although none of the included observational studies have reported a cost calculation, it may be inferred that they would be a modest saving because of lower direct and indirect costs of occupying a hospital bed. Although none of the studies had reported on the actual duration of antibiotic therapy, it is almost self-evident that a shorter duration of antibiotics would cost less than the standard duration of antibiotics. Thus, a shorter duration of antibiotics may reduce costs in the short term.

It is not possible to comment on whether the short duration of antibiotics will reduce costs in the long term. With the current state of evidence available from literature, the balance of effects does not favour either a short course of antibiotics or a standard course for the critically important outcomes. Since substantial harm in the form of chronic renal failure (which would require an increased cost of care), and definite relapse (which would require re-hospitalization and re-treatment) cannot be excluded, the possible short-term cost savings may be nullified in the long run.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: No Included studies

Shorter duration of antibiotics and lesser days of hospitalization are expected to decrease costs. However, none of the included observational studies reported a cost calculation. A wide variety of antibiotics are used in the treatment of UTI in newborn infants. The per-day cost of a hospital bed is also extremely variable, depending upon the level of care. Therefore, it is difficult to simulate the expected difference in the cost of care.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: Does not favour either the intervention or the comparison

Cost-effectiveness was not studied in any of the included studies. The cost-effectiveness of the intervention does not favour either the intervention or the comparison because, apart from a modest decrease in the duration of hospitalization, the quality of evidence for all critically important and important outcomes is very low, and the effect includes both substantial benefit

and substantial harm. The issue of cost-effectiveness would arise only if it were possible to conclude that the intervention provides at least some benefit for critical outcomes.

Equity (what would be the impact on health equity?)

Judgement: Varies

The impact on health equity would be variable. With the very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm. If the truth is that a short course of antibiotics reduces the duration of antibiotic therapy and duration of hospitalization without a substantial increase in mortality or relapse of UTI, the intervention would increase health equity. However, if the truth is that a short course of antibiotics increases mortality or relapse, the intervention would reduce health equity, as substantially more cost and resources would be required to manage episodes of relapse and subsequent complications.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: Varies

With the very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm. In this context, the acceptability of a short course of antibiotics would vary between the key stakeholders.

Feasibility (is the intervention feasible to implement?)

Judgement: Yes

In principle, the intervention (short course of antibiotics) is very feasible to implement because it requires fewer resources. However, the issue of feasibility does not arise at present. With the very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm with either the short course or standard course of antibiotics.

RECOMMENDATION

12. The guidelines group suggests NOT to use a shorter course of antibiotics (typically ≤10 days) in newborn infants with uncomplicated% urinary tract infection (UTI); these neonates may preferably be treated using a standard longer course of antibiotics (typically 14 days).

Weak recommendation, Very low certainty of evidence

% Uncomplicated UTI defined as UTI WITHOUT anatomical abnormalities of kidney, ureters, urinary bladder, abscesses, pyonephrosis

Justification

Although currently, there is no prescribed standard of care, most units tend to prescribe antibiotics for 10-14 days for uncomplicated UTI in neonates, and over the years this has become default duration, despite the lack of evidence to back it. Therefore, in the light of this, the panel feels that, to shorten the duration of antibiotics, it would be necessary to demonstrate that shorter duration of antibiotics is not inferior to the standard duration with

respect to mortality, relapse rates and neurodevelopmental impairment. Since the evidence in literature is inconclusive about these critical outcomes, any kind of recommendation in favor of the intervention (short course) is not possible. Considering that the evidence is inconclusive and there is weak evidence in favor of shorter duration of hospitalization, the panel decided to make a weak recommendation against the intervention.
Overall, the panel's recommendation is to continue with the current default practice of 10-14 days of intravenous antibiotics for uncomplicated UTI, until more robust evidence is available.
Desirable Effects :The quality of evidence for the duration of hospitalization is low.
Undesirable Effects :The quality of evidence for critical outcomes such as mortality at various time points was not available. The quality of evidence for a critical outcome such as definite culture-proven relapse of UTI was very low because of the serious risk of bias arising from retrospective cohort studies
Certainty of evidence: Evidence was of very low quality

Subgroup considerations

No subgroup analyses were performed. However, newborn babies with complicated UTI: such as pyelonephritis, associated meningitis, associated renal anomalies, and multi-organ dysfunction will need a longer duration of antibiotics. Hence the duration of antibiotics may be decided by the clinical condition and response of the therapy in these specific circumstances.

Implementation considerations

As things stand, the panel does not recommend a short course of antibiotics for bacteriologically proven UTI. If at a future date, robust evidence emerges that short-course antibiotic therapy is associated with substantially greater benefit than harm, then implementation of short-course antibiotic therapy is unlikely to require any special prerequisites, training, infrastructure, or expenditure.

Monitoring and evaluation

Since the panel gives a conditional recommendation against the intervention (short-course antibiotics) and advises continuation of the standard (10 to 14 days) course of antibiotics, there is no extra monitoring or evaluation that needs to be done, over and above what is currently being done.

Research priorities

Given the paucity of evidence, the panel recommends that a large multicentre non-inferiority open-label, randomized controlled trials must be conducted to compare the impact of shorter courses of antibiotics versus standard courses of antibiotics on critical and important outcomes in uncomplicated, culture-proven UTI in newborn infants.

***Practice Question 13*: Among newborn infants with proven fungemia, is a fixed duration of anti-fungals (typically 14-21 days) is non-inferior to 14 days anti-fungals after last negative culture?**

Pico question

P= newborn infants with proven fungemia
I= fixed duration antifungals (14-21 days)
C= at least 14 days antifungal after culture negative
O= Mortality during hospital stay; Mortality within day 28 of life; Mortality by 12 months of corrected age; Relapse with culture-positive sepsis or meningitis or urinary tract infection; Relapse with culture-negative sepsis or meningitis or urinary tract infection; Duration of antibiotic therapy; Duration of hospital stay; Serious adverse drug reactions; Cost of care.

Summary of evidence

No eligible studies could be found.

Summary of judgements

Problem (is the problem a priority?)

Judgement: Yes

Invasive fungal infections are increasing in the NICU due to the survival of more and more preterm babies (124, 125).The incidence of fungal infections in VLBW is 1 to 4 %, ELBW is 2 to 8 % and in extremely low birth weight (< 750 gram) or gestation < 26 weeks is 20% (126).The rate of systemic fungal infections as reported in the DeNIS study group from India is 22.7 % of all culture-positive infections in the outborn cohort from a teaching hospital in India (127).The distribution for fungal sepsis in NICU was predominantly *C. albicans* (63%), *C. parapsilosis* (29%), *C. glabrata* (6%), and other *Candida* species (3%) (128).The mainstay of treatment in these conditions is Amphotericin B and Fluconazole. The duration of treatment in neonates with proven fungal infections is not clear and clinicians are faced with a dilemma regarding the duration if 14-21 days is adequate or treatment should be 14 days after the cultures are negative. The evidence for either practice seems to be scarce.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: Don't know

The critically important desirable effect with a shorter duration of antifungal therapy would be a reduction: in the duration of antibiotic therapy, in the duration of hospital stay, serious adverse drug reactions, and cost of care. These benefits should come without any increase in risks of mortality or recurrence of culture-positive or culture-negative sepsis or meningitis or urinary tract infection. RCTs or observational studies that compared these outcomes are not available.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: Don't know

The critically important undesirable effect with a shorter duration of antifungal therapy would be an increase in risks of mortality or recurrence of culture-positive or culture-negative sepsis or meningitis or urinary tract infection.

In the proposed intervention as antifungal treatment administered for 14-21 days compared with 14 days after culture-negative infections, one may feel the risk of recurrence or relapse of fungal infection and chances of higher mortality in the first month after discharge.
RCTs or observational studies that compared these outcomes are not available.

Certainty of evidence (what is the overall certainty of the evidence of effects?)

Judgement: No Included studies

We were unable to find any systematic review or RCTs or observational studies comparing the modalities of treatments in terms of duration of antifungal therapy to see the efficacy, safety, or relapse rates in newborn infants with invasive fungal infections.

It is important to note that for all the critical and important outcomes assessed for writing these guidelines, we could find 4 guidelines (129-134) and one review of guidelines (135) with either serious or very serious risk of bias. Cochrane systematic reviews on antifungal therapy have not addressed the question under consideration (136, 137). IDSA 2016 guidelines have been endorsed by the AAP and the PIDS (132).

IDSA 2016 guidelines in its recommendation, elaborates that, "The recommended duration of therapy for candidemia without obvious metastatic complications is for 2 weeks after documented clearance of Candida species from the bloodstream and resolution of signs attributable to candidemia (strong recommendation; low-quality evidence). These recommendations are based on the expert opinion of the IDSA group.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: No Important uncertainty or variability

As guidelines authors, we are of the view that the outcomes: mortality during the hospital stay, mortality within day 28 of life, mortality by 12 months of corrected age, relapse with culture-positive sepsis or meningitis or urinary tract infection, relapse with culture-negative sepsis or meningitis or urinary tract infection, duration of antibiotic therapy, duration of hospital stay, serious adverse drug reactions, and cost of care are the critical or important outcomes of this guideline. These are valued highly by all the stakeholders including patients, families, clinicians, and policymakers. Therefore, we do not consider that there is any important uncertainty about the importance of this outcome.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: Don't know

Not possible to assess due to the lack of any systematic review, or RCTs, or observational studies comparing the modalities of treatments under consideration.

Resources required (How large are the resources required?)

Judgement: Moderate savings

By reducing the duration of antifungal antibiotic therapy, duration of hospital stay, serious adverse drug reactions, and cost of care, improving antifungal stewardship would help in reducing the economic burden on health care.

Teaching, training of human resources, surveillance, and multi-disciplinary involvement would help optimize the outcomes in the management of sick neonates.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: No Included studies

No evidence is available regarding the certainty of the evidence of the required resources. The cost of the treatment depends not only on the availability of human resources and their

training (which may be fixed) but also on other adjunct costs and supportive care which are variable and need to be studied.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: No Included studies

The Cost-effectiveness of the treatment approach has not been investigated in any randomized controlled trial or observational study.

Equity (what would be the impact on health equity?)

Judgement: Uncertainty

No studies are available in newborn infants that have studied health equity aspects with different durations of antifungal therapy under consideration.

Giving antifungal therapy for 14 days after the cultures are negative versus giving for a fixed 14-21 days may be associated with less or more duration of treatment thereby making this intervention cost-effective or cost ineffective. Uncertainty remains.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: Probably Yes

Given the need for a lesser duration of treatment and unnecessary intravenous cannulation and rooming-in of neonates with mothers, the intervention seems acceptable to all the stakeholders, provided the intervention works.

Feasibility (is the intervention feasible to implement?)

Judgement: Probably Yes

The intervention is feasible to implement considering the advantages offered to all stakeholders. Government programs like NSSK along with medical institutional programs such as the sick newborn care course and preterm training package can be used as platforms for widespread dissemination of essential teaching and training of neonatal staff posted in all secondary and tertiary care units for efficiently managing these neonates.

RECOMMENDATION

13a. The guidelines group suggests using antifungal therapy for 14 days *after* documented clearance of Candida species from the bloodstream and resolution of signs attributable to candidemia (and not for a pre-fixed duration - typically 14-21 days).

Weak recommendation, Not graded (Expert consensus)

13b. The group suggests a longer duration of antifungal therapy in case of a deep-seated tissue infection or metastatic complication based on the site of infection, the patient's response to treatment, and the resolution of signs and symptoms.

Weak recommendation, Not graded (Expert consensus)

Justification

Overall justification

Overall, the duration of treatment should be made in the wake of clinical condition, the extent of the infection, response to both clinical and microbiological (repeat cultures) results.

Detailed justification

Desirable Effects

Reduction in antifungal usage rates and more rational usage may result in decreased hospital stay without any impact on mortality.

Undesirable Effects

Possibility of missing potentially sick neonate with deep-seated infections because of inadequate duration of the antifungal drug, and causing adverse outcomes in form of meningitis, respiratory/ and cardiovascular failure, and in worst-case scenario causing mortality.

Subgroup considerations

Newborn babies with invasive fungal disease and not having localized deep-seated infections such as meningitis, abscesses in lungs, brain, kidneys, or bones may be safely treated for 14 days after the cultures are negative may be a reasonable approach.

Implementation considerations

Adequate training facilities need to be created uniformly across secondary and tertiary setups along with the building of standardized treatment protocols for uniform treatment.

Monitoring and evaluation

Careful treatment protocol regarding the management of neonates with antifungal agents needs to be established uniformly in the management of all high-risk babies across the country so that evidence can be strengthened and further refined for generalized applicability.

Research priorities

There is an urgent need to conduct multicentre RCTs to answer the question under consideration:

Should fixed duration antifungals (14-21 days) vs. at least 14 days antifungal after culture-negative be used in newborn infants with proven fungemia?

When it comes to infections due to Candida species this can be studied in two subgroups of *Candida albicans* and Non-*albicans* if species identification is feasible.

***Practice Question 14*: Among Newborn infants in SNCU with probable sepsis/meningitis, is a combination of antibiotics Cefotaxime + Amikacin or higher superior compared to a standard course of Ampicillin plus Gentamicin?**

Pico question

P= Neonates in SNCUs with probable sepsis/meningitis ; I= Cefotaxime + Amikacin or higher antibiotics; C= Ampicillin + Gentamicin; O= Mortality in hospital; Mortality during the first 28 days of life; Mortality within 12 months of corrected age; Relapse with culture negative (probable) sepsis / meningitis; Moderate or severe neurodevelopmental impairment at or after 12 months of age (Either of seizures needing more than one anticonvulsant during follow-up or cerebral palsy or cognitive disability or blindness or deafness); Death or moderate or severe neurodevelopmental impairment at or after 12 months of age (Either of seizures needing more than one anticonvulsant during follow-up or cerebral palsy or cognitive disability or blindness or deafness); Cost of care; Duration of hospital stay; Serious adverse reactions

Summary of evidence

Table 12 shows the summary of evidence.

Table 12: Summary of findings table

Patient or population: probable sepsis/meningitis in neonates in SNCU
Setting: Neonates admitted in SNCU
Intervention: Cefotaxime + Amikacin or higher antibiotics
Comparison: Ampicillin + Gentamicin

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Ampicillin + Gentamicin	**Risk with Cefotaxime + Amikacin or higher antibiotic**				
Mortality in hospital	14 per 1,000	**21 per 1,000** (3 to 122)	**RR 1.50** (0.25 to 8.84)	290 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,d]	Mortality during hospital stay was not significantly different between those who received ampicillin gentamicin and higher antibiotics
Mortality during the first 28 days of life	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	Outcome not reported in any study
Mortality within 12 months of corrected age	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	Outcome not reported in any study
Relapse with culture negative (probable) sepsis / meningitis	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	290 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,e]	There were no relapses observed in the included study

Moderate or severe neurodevelopmental impairment at or after 12 months of age (Either of seizures needing more than one anticonvulsant during follow-up or cerebral palsy or cognitive disability or blindness or deafness)	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	Outcome not reported in any study
Death or moderate or severe neurodevelopmental impairment at or after 12 months of age (Either of seizures needing more than one anticonvulsant during follow-up or cerebral palsy or cognitive disability or blindness or deafness)	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(0 studies)	-	Outcome not reported in any study
Cost of care	The mean cost of care was **0**	not pooled	-	(0 studies)	-	Outcome not reported in any study
Duration of hospital stay	The mean duration of hospital stay was **0**	**0** (0 to 0)	-	(0 studies)	-	Outcome not reported in any study
Serious adverse reactions	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	290 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c,f]	There were no serious adverse drug reactions in the included study

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

Explanations

a. There were 14 dropouts in penicillin group and 5 drop outs in ceftriaxone group leading to attrition bias, for which we downgraded the evidence. Although the study was not blinded, we did not downgrade for lack of blinding as blinding was not possible due to nature of the intervention (no of doses of antibiotics).

b. We did not downgrade for inconsistency because only one study included

c. Downgraded for indirectness because the trial compared Procaine penicillin plus gentamicin versus ceftriaxone

d. 95% CI 0.25 to8.84 e. 95% CI is 0.89 to 3.23 f. 95% CI could not be calculated because there were no events reported in either arm. Hence downgraded for imprecision.

Summary of judgements

Problem (is the problem a priority?)

Judgement: Yes

Sepsis remains to be a major cause of mortality and morbidity in neonates. Of the 3 million annual cases of neonatal sepsis globally, India has the maximum number of clinical sepsis cases (4). An ideal empiric antibiotic should cover most of the common pathogens without providing unwarranted selection pressure for antibiotic resistance (138).

As per WHO 2016 guidelines (3)(139), the antibiotic regimen of choice to treat serious bacterial infection in infants less than 60 days in LMIC when referral is not possible are *Option1:* IM gentamicin 5–7.5 mg/kg (for low-birth-weight infants gentamicin 3–4 mg/kg) once daily for 7 days and twice daily oral amoxicillin, 50 mg/kg per dose for 7 d. *Option2:* IM gentamicin 5–7.5 mg/kg (for low-birth-weight infants gentamicin 3–4 mg/kg) once daily for 2 days and twice daily oral amoxicillin, 50 mg/kg per dose for 7 d. Special newborn care units (SNCU) have been widely established in various districts all over India to provide level II neonatal care. Since data on organism prevalence and antibiograms are scarce from SNCUs, the choice of first line empiric antibiotics for suspected neonatal sepsis/meningitis is very variable and includes, ampicillin plus gentamicin, cefotaxime, amikacin.

Since in many centres it is a common practice to use broader spectrum antibiotics to treat neonatal sepsis, it is of concern to understand the efficacy of first line antibiotics with narrow spectrum like penicillin and aminoglycosides as compared to cephalosporin's or higher antibiotics. There is also concern about the changing organism profile and resistance pattern with use of higher antibiotics everywhere. In a survey conducted by the panellists, the comparison of cefotaxime amikacin or higher antibiotics versus ampicillin gentamicin for probable sepsis or meningitis in SNCU was rated to be extremely important. In view of all the above facts, this problem is considered a priority.

Desirable outcomes (how substantial are the desirable anticipated effects?)

Judgement: Varies

The important desirable effects with using higher antibiotics in empiric regimen for treating probable neonatal sepsis are improved clinical outcomes like decrease in mortality (in hospital, in neonatal period and in 12 month follow up), neurodevelopmental impairment, relapses, hospital stay, duration of treatment and hence cost of care.

Only one eligible RCT was included in the analysis (140).The absolute effect on mortality during hospital stay ranged from 3 fewer deaths to 122 more deaths per 1000 subjects. The risk estimates are imprecise and include no effect, substantial benefit, and substantial harm. Quality of evidence was very low because of the serious risk of bias and imprecision.
There were no relapses noted in the included RCT.
Other outcomes were not reported by any studies.

Undesirable outcomes (how substantial are the undesirable anticipated effects?)

Judgement: Varies

The important undesirable outcomes with using higher antibiotics are increase in the incidence of multi-drug resistant (MDR), pan-drug resistant (PDR) an extremely drug resistant (XDR) bacteria, serious adverse drug reactions and increase in the incidence of fungal sepsis. None of the studies in literature search reported these outcomes.

Certainty of evidence (what is the overall certainty of the evidence of effects?)

Judgement: Very low

The overall certainty of the evidence of effects is very low. Since only one RCT was eligible for inclusion there was serious risk of bias, imprecision and inconsistency making the quality of evidence very low. Only one critical outcome and one important outcome were reported. The risk estimates were also imprecise. No undesirable outcomes were reported.

Values (is there important uncertainty about or variability in how much people value the main outcomes?)

Judgement: No important uncertainty or variability

Since neonatal sepsis is managed with broad spectrum antibiotics in many centres and there is emergence of bugs resistant to narrow spectrum antibiotics, using broad spectrum antibiotics in empiric regimen would logically lead to improved clinical outcomes like decrease in mortality, neurodevelopmental impairment, relapses and complications of sepsis. However, in the absence of good quality evidence, recommending such a practice might increase antibiotic misuse thereby worsening antibiotic resistance.

The guideline panel considers that there is no important uncertainty of variability in how much people value the main outcomes, i.e. mortality at various time points and moderate to severe neurodevelopmental impairment by 12 months of post-term corrected age and definite relapse of culture proven sepsis or meningitis. Moderate to severe neurodevelopmental impairment poses a substantial and lifelong burden on the family, hospitals, the health system, and society (78).Thus, the panel believes neurodevelopmental impairment is also a universally acknowledged critically important outcome. Relapses with culture proven sepsis necessitate rehospitalisation, painful procedures, re-exposure to antibiotics and the risk of superinfections. Thus, avoiding relapses is important from the point of view of all stakeholders.

Balance of effects (does the balance between desirable and undesirable effects favoured the intervention of the comparison?)

Judgement: Does not favour either the intervention or the comparison

The balance between desirable and undesirable effects does not favour either the intervention or the comparison. Evidence for the desirable outcomes are of very low quality because of serious risk of bias and very serious imprecision. There was no evidence for undesirable outcomes. 95% confidence limits of the absolute effects of using cefotaxime amikacin or higher antibiotics for probable sepsis includes no effect, substantial benefit, and substantial harm for all the critical outcomes evaluated. Overall, there is a paucity of evidence and literature, with only one small randomized controlled trial addressing the issue, and several critically important outcomes remaining unaddressed.

Resources required (*How large are the resources required?)*

Judgement: Varies

There is currently no evidence whether using broad spectrum antibiotics in empiric regimen for probable sepsis would alter the resource requirements. Short term outcomes like duration of hospital stay, cost of care were not reported in any study. Since evidence is lacking for outcomes like relapses, moderate to severe neurodevelopmental impairment, it is not possible to comment on the effects on long term resource requirements as well.

Certainty of evidence of required resources (What is the certainty of the evidence of resources required?)

Judgement: No included studies

Since there were no included studies that reported on required resources with the intervention, no evidence is currently available on the same.

Cost-effectiveness (does the cost-effectiveness of the intervention favour the intervention or the comparison?)

Judgement: No included studies

Cost effectiveness was not studied in the included randomized controlled trial. There is no evidence that the intervention provides benefit for any of the critical outcomes. The quality of evidence is also very low. Hence it is not possible to comment on the cost effectiveness.

Equity (what would be the impact on health equity?)

Judgement: Varies

With the very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm. Since the cost of care may increase or decrease in long run based on the effect on critical outcomes, broad spectrum antibiotics may decrease or increase the health equity accordingly. In the absence of evidence for the same, it is not possible to comment on health equity.

Acceptability (is the intervention acceptable to key stakeholders?)

Judgement: Varies

With the very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm. In this context, the acceptability of using cefotaxime plus amikacin or higher antibiotics in treating probable sepsis would vary between the key stakeholders.

Feasibility (is the intervention feasible to implement?)

Judgement: Yes

With the very low-quality evidence currently available, it is not possible to exclude substantial benefit or substantial harm with either higher antibiotics or ampicillin. Hence, the issue of feasibility does not arise at present.

RECOMMENDATION

14. The guidelines group suggests NOT to use Cefotaxime + Amikacin or higher broad-spectrum antibiotics for probable sepsis or meningitis in neonates *admitted to* special care neonatal units (*SNCUs*); these neonates may preferably be treated with the WHO recommended first-line antibiotics of Ampicillin + Gentamicin.

Weak recommendation, Very low certainty of evidence

Justification

Overall justification

WHO recommends ampicillin or benzyl penicillin plus gentamicin as the first line of treatment for serious bacterial infection in infants < 60 days in LMIC when referral is not possible. Therefore, in the view of this panel, to recommend cefotaxime plus amikacin as empiric choice of antibiotics for probable sepsis/meningitis in neonates in SNCU it would be necessary to demonstrate that it is superior to ampicillin + gentamicin with respect to mortality, relapse rates and neurodevelopmental impairment, is cost effective and feasible and that it does not lead to increase in antibiotic resistance. Since the evidence in literature is inconclusive about these critical outcomes, any kind of recommendation in favour of the intervention (cefotaxime plus amikacin or higher antibiotics) is not possible. Considering that the evidence is inconclusive, the panel decided to make a weak recommendation against the intervention.

Detailed justification

Desirable Effects : Lack of evidence for desirable effects like decrease in mortality
Undesirable Effects : No undesirable effects were reported
Certainty of evidence : Evidence was of very low quality
Cost effectiveness :No evidence for the same

Subgroup considerations

No subgroup analysis was performed

Implementation considerations

The panel suggests against administering cefotaxime plus amikacin or higher antibiotics as first line antibiotics for probable sepsis for neonates admitted in SNCU. If, at a future date, evidence emerges favouring cefotaxime plus amikacin, then implementation considerations may include expenditure (cost higher than ampicillin gentamicin). However, no special prerequisites or training would be needed.

Monitoring and evaluation

Since the panel suggests not administering cefotaxime plus amikacin and advises continuation of ampicillin plus gentamicin, there is no extra monitoring or evaluation that needs to be done, over and above what is currently being done.

Research priorities

Given the paucity of evidence, the panel recommends that large multi-centric superiority open-label, randomized controlled trials must be conducted to compare cefotaxime plus amikacin or higher antibiotics versus ampicillin plus gentamicin for neonates admitted in SNCUs with probable sepsis/meningitis. The panel recommends a survey to audit what proportion of SNCU's are currently using ampicillin plus gentamicin versus cephalosporins as first-line antibiotics for neonatal sepsis.

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Annexures

Annexure 1 – List of questions circulated to participants for rating importance

Annexure 2 - Search terms used in Pubmed, Embase and Cochrane Database of Systematic Reviews

Annexure 3 - Flow charts of search strategies

Annexure 4 - PRISMA flow diagrams

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