Clinical Practice Guidelines *for* the Screening, Diagnosis, Treatment and Prevention *of* Neonatal Sepsis

2019

ABBREVIATIONS

AAP	American Association of Pediatrics
ANC	absolute neutrophil count
CBC	complete blood count
CI	confidence interval
CNS	central nervous system
CPG	clinical practice guideline
CRP	C-reactive protein
CSF	cerebrospinal fluid
DOH	Department of Health
DVET	double volume exchange transfusion
EOS	early-onset sepsis
FFP	fresh frozen plasma
GBS	Group B Streptococcus
IT	immature to total neutrophil count
IV	intravenous
LBW	low birth weight
LOS	late-onset sepsis
LR	likelihood ratio
LRC	low risk criteria
MCNAP	Mother and Child Nurses' Association of the Philippines
NICE	National Institute for Health and Care Excellence
NICU	neonatal intensive care unit
NPV	negative predictive value
OR	odds ratio
P/IVH	periventricular/intraventricular hemorrhage

PAFP	Philippine Academy of Family Physicians
PDA	patent ductus arteriosus
PGH	Philippine General Hospital
PHIC	Philippine Health Insurance Corporation
PICO	population, intervention, comparator, outcome
PIDSP	Pediatric Infectious Disease Society of the Philippines
POGS	Philippine Obstetrical and Gynecological Society
PPV	positive predictive value
PSNbM	Philippine Society of Newborn Medicine
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	randomized controlled trial
ROM	rupture of membranes
RR	risk ratio
SBI	systemic bacterial infection
Sn	Sensitivity
Sp	Specificity
UHC	Universal Health Care
UTI	urinary tract infection
VLBW	very low birth weight
WBC	white blood cell

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How To Use This Document

This CPG is a *de novo* systematic synthesis of evidence to address eleven (11) questions which emerged from the current clinical practice in newborn care in the Philippines. This guideline can be appreciated fully when it is read sequentially as it appears here in the document.

An overview of goals and focus of this guideline can be found in the *Introduction.* The whole process of CPG formulation is written in the *Guideline Development Methods* from page 11.

Many users of this guideline would be particularly interested in the evidence gathered and recommendations formulated. Evidence review related to diagnosis and screening precedes the review summary of treatment and prevention of neonatal sepsis. These contents appear as a summary in the *Evidence and Recommendations* starting on page 16. For an in-depth analysis of each evidence base, the sources are listed in the *References*.

 The electronic version of this material can be accessed online in websites of PSNbM and PIDSP while printed copies are available in offices of these medical societies.

Queries, suggestions and other concerns regarding this CPG may be directed to the DOH office by email.

ACKNOWLEDGMENT

This project would not have been possible without the initiative and financial support from the Department of Health. The DOH neither imposed any condition nor exerted any influence on the operations and in the formulation of the final output.

The University of the Philippines - Department of Clinical Epidemiology (UP-DCE) and Philippine Society of Newborn Medicine (PSNbM) undertook the extensive technical work in (1) searching and synthesizing the evidence while ensuring objectivity in each stage of the process, (2) presenting the evidence in the panel discussion and (3) documenting and writing the final report. They were also indispensable in carrying out the legwork, coordinating among various individuals, groups and committees and facilitating the *en banc* meeting. The CPG Steering Committee, composed of members of the PSNbM and PIDSP, was responsible for overall organization and management, and is accountable for the quality of the CPG.

Lastly, this guideline is invaluable because of the contribution and participation of panelists from different sectors of healthcare who committed their time and effort to sharing their knowledge, experience and expertise, in analyzing the scientific evidence and their values and preferences in formulating the recommendations with consideration of patients and the current healthcare system in the country.

DISCLAIMER

This guideline is intended to be used by specialists, general practitioners, allied health professionals who are largely involved in or providing newborn care. Although adherence to this guideline is encouraged by the DOH, PSNbM and PIDSP, it should not restrict the clinicians in using their own clinical judgment and in considering patient's values, needs and preferences while handling individual cases. Clinicians, e.g. general pediatricians or neonatologists must always exercise sound clinical decision-making as the individual patient's history and current physical status dictate and while their responses to treatment may vary.

Policy-makers and payors can also utilize this CPG but nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this guideline should not also be treated as strict rules to base legal action on.

Developers of this CPG are cognizant of its limitations. Evidence summaries are based on best available scientific evidence as of the time of its formulation. However, certain aspects of assessment and management may not have been addressed by the clinical trials and observational studies and as such evidence bases are therefore not all inclusive. Considerations on these aspects were still deemed important in the current contexts of newborn care.

EXECUTIVE SUMMARY

This Clinical Practice Guideline (CPG) for the Screening, Diagnosis, Treatment and Prevention of Neonatal Sepsis is an output of the Neonatal Sepsis Task Force, and constitutes a joint undertaking of the Philippine Society of Newborn Medicine (PSNbM) and the Pediatric Infectious Disease Society of the Philippines (PIDSP). It was developed *de novo*, i.e. it is not an adaptation of existing clinical practice guidelines developed by other entities.

The CPG provides eleven (11) practice recommendations on prioritized interventions in in the screening, diagnosis, treatment and prevention of neonatal sepsis and sepsis-related deaths. It is not meant to supplant guidance on conventional management of neonatal sepsis, i.e. timing of diagnostic work-up, choice of empirical antibiotics, monitoring of the newborn with suspected sepsis, basis for shifting antibiotics, etc.

Recommendations are based on the appraisal of the best available evidence on each of the eleven identified clinical questions. The CPG is intended to be used not only by pediatricians, neonatologists, obstetricians, and perinatologists but also by family medicine and general practitioners who care for newborns in both hospitals and birthing centers. The guideline development process followed the widely accepted Grading of Recommendations, Assessment, Development and Evaluation or the GRADE approach and included 1) identification of critical questions and critical outcomes, 2) retrieval of current evidence, 3) assessment and synthesis of the evidence base for these critical questions, 4) formulation of draft recommendations, 5) convening of a multisectoral stakeholder panel to discuss values and preferences and assess the strength of the recommendations, and 6) planning for dissemination, implementation, impact evaluation and updating.

The recommendations in this CPG shall hold until such time that technology, patient and provider preferences, or new evidence provide the motivation for reviewing and updating the guidelines.

Table 1. Summary of Recommendations

Recommendation	Strength of Panel Recommendation	Quality of Evidence
No recommendation can be made at this time for use of an early onset neonatal sepsis calculator for neonates delivered to mothers with UTI within two weeks prior to delivery.	Not applicable	Very Low
Among newborns with risk factors, a single abnormal parameter in a CBC done within the 6th-24th hour of life should not be used alone to diagnose sepsis.	Strong	High
A combination of CBC and any single quantitative CRP is not accurate in diagnosing sepsis in asymptomatic newborns but may be more useful in ruling out sepsis when done after 24 hours of life.	Conditional	Low
a. Among newborns with early onset sepsis or EOS, a blood culture, when positive, is useful to predict CNS infection and should warrant lumbar puncture.	Strong	Low
b. Among newborns with late onset sepsis or LOS, a blood culture result is not useful in predicting CNS infection. Therefore, a lumbar puncture is still recommended.	Conditional	Very Low
Universal culture-based screening of women near term should not be performed to prevent early-onset GBS disease.	Strong	Very Low
Among newborns with severe sepsis, double volume exchange transfusion or DVET as an adjunct treatment is recommended.	Conditional	High
The use of fresh frozen plasma among newborns with sclerema neonatorum in order to decrease morbidity and mortality is not recommended.	Strong	Low
Antibiotic prophylaxis for asymptomatic newborns delivered meconium stained is not recommended.	Strong	Low
A 5-day course over a 7-day course of intravenous antibiotic is not recommended for newborns with clinical sepsis who improve after initial antibiotic therapy.	Strong	Low to Very Low
Among healthy-looking newborns presenting with fever alone, 20% of them will develop sepsis.	Not applicable	Low

Recommendation	Strength of Panel Recommendation	Quality of Evidence
Among newborns with no risk factors for infection presenting with isolated jaundice, the risk of sepsis is 3.9%.	Not applicable	Low

INTRODUCTION

Sepsis has been a global public health priority because of its fatal outcomes in extreme age groups including newborns [1]. In a recent pooled study, 11-19% mortality was estimated among 2202 neonates for each 100,000 live births that became septic [1]. Although this data only covered those newborns from middle-to-high income countries, mortality and morbidity cases among infants in developing countries caused by neonatal sepsis are also still reported to be relatively high [2,3].

For the year 2017, neonatal sepsis (together with neonatal tetanus) ranked third among the causes of neonatal mortality at 14%, after preterm birth complications (31%) and intrapartum-related events (24%), according to estimates generated by the WHO and Maternal and Child Epidemiology Estimation Group (MCEE) 2018 [4]. It has caused a heavy burden across all developed and developing countries. In 2013, the Philippines Department of Health reported that neonatal sepsis was the second leading cause of infant mortality at 12.4%.

Because of the huge burden of neonatal sepsis in the Philippines in terms of morbidity and mortality, and a large variation in practice, this guideline is imperative. The lack of available guidelines on local concerns such as its risk factors (meconium stained amniotic fluid, maternal urinary tract infection), clinical manifestations (isolated fever and jaundice), preventive measures (GBS screening), affordable diagnostic tools (complete blood count, C-reactive protein, CSF analysis) and adjunctive treatment (fresh frozen plasma and double volume exchange transfusion) encourages the formulation of this CPG. Likewise, the duration of antibiotic treatment will be tackled to address judicious use and socioeconomic concerns.

In response to these pressing needs, under the guidance of the Department of Clinical Epidemiology of the University of the Philippines College of Medicine, the Neonatal Sepsis Task Force was convened jointly by the Philippine Society of Newborn Medicine and the Pediatric Infectious Disease Society of the Philippines. The CPG on Neonatal Sepsis was one of 5 prioritized CPGs for development in the first round of DOH-supported CPGs, mandated in the Implementing Rules and Regulations of Republic Act 11223 or the “Universal Health Care (UHC) Law.

This CPG is expected to reduce practice variation, discourage the use of procedures that are of minimal or questionable benefit especially if with associated harm, increase the use of services that are effective but underused, and target populations most likely to benefit from those services. It has the potential to impact neonatal sepsis management nationwide for years to

come and it is our hope that this shall be regarded as a source of valid recommendations that ensure adherence to standards of patient care and safety.

Target users of this CPG include but are not limited to PSNbM, PIDSP and PPS members and referring physicians, training institutions, regulatory agencies and payors, patients, the general public and industry partners.

GUIDELINE DEVELOPMENT METHODS

Organization of the Process

First, the Lead CPG Developer created a Steering Committee from the members of PSNbM, members of PIDSP and practitioners from different hospitals providing neonatal care. The Steering Committee was tasked to oversee the CPG formulation process including but not limited to formulation of PICO questions and setting up working groups and their composition (i.e. Evidence Review Experts and Consensus Panel) [1].

The Evidence Review Experts were tasked to appraise and summarize the evidence searched systematically, review existing CPGs, and draft the evidence-based recommendations [1].

Lastly, the Consensus Panel reviewed the evidence summaries and draft recommendations prior to and during an *en banc* meeting. They prioritized the critical and important outcomes and voted on each recommendation and on its strength. Should there have been no consensus reached during the *en banc* meeting, they agreed to participate in a modified Delphi activity, if needed [1].

Creation of the Evidence Base

The EREs were set to perform systematic searches in electronic databases and local databases using keywords based on PICO (MeSH and free text) set for each question. Handsearching references of articles included were also done to ensure a comprehensive search. Authors of related articles were also contacted via email and/or phone call to identify other research studies for appraisal.

Evidence reviewers appraised the directness, methodological validity, results and applicability of each relevant article included [1]. RevMan version 5.3 and/or GRADEPro was used for quantitative synthesis of important clinical outcomes identified for each therapy question. The team constructed evidence summaries for each of the 11 research questions, summarizing the

trade-offs between benefit and harm. The Quality of Evidence was assessed according to Table 2.

Table 2. Basis for Assessing the Quality of the Evidence using GRADE Approach

Observational studies	Quality of the Evidence	Randomized trials
Extremely strong association and no major threats to validity	High (Further research unlikely to change our confidence in estimate of effect)	No serious flaws in study quality
Strong consistent association and no plausible confounders	Moderate (Further research is likely to have an important impact)	Serious flaws in design or execution or quasi-experimental design
No serious flaws in study quality	Low (Further research is very likely to have an important impact)	Very serious flaws in design or execution
Serious flaws in design and execution	Very low (The estimate of effect is very uncertain)	Very serious flaws and at least one other serious threat to validity
Additional factors that lower quality of the evidence are: ● Important inconsistency of results ● Some uncertainty about directness ● High probability of reporting bias ● Sparse data ● Major uncertainty about directness can lower the quality by two levels Additional factors that may increase quality are: ● All plausible residual confounding, if present, would reduce the observed effect ● Evidence of a dose-response gradient		

Composition of the CPG Panel

The Steering Committee convened the Consensus Panel (CP) with consideration of possible conflicts of interests of each panel member. To ensure fairness and transparency, the composition was guided by the recommendations of DOH [1]. Content and methodology experts as well as other key stakeholders were invited to join the CP. The key stakeholders included policy-makers, patient advocates, allied medical practitioners and physicians from different settings (e.g. government hospitals, private practice, community). The physicians who were invited were mostly practicing general pediatricians, neonatologists, obstetrician-gynecologists, family and community physicians, infectious disease specialists because they are the direct users of this guideline.

Formulation of the Recommendations

Draft recommendations, which are statements regarding actions with direct clinical implications related to the question answered, were formulated based on the quality of evidence, trade-offs between benefit and harm and uncertainty due to research gaps. These recommendations, together with the evidence summaries, were presented in the *en banc* meeting.

The recommendation for each question and its strength was determined through voting. A winning vote or a consensual decision was considered to be 75% of all those CP members who voted [1]. If consensus was not reached in the first voting, questions and discussions were encouraged. Two further rounds of voting on an issue were conducted. Should there have been no consensus after the three rounds, a stalemate was to be declared and the issue decided at a later date using a modified Delphi technique to reach consensus. Evidence-based draft recommendations were also revised based on input arrived at by consensus in the *en banc* discussions.

Managing Conflicts of Interest

The Steering Committee facilitated the whole CPG formulation process but their members had no direct participation in assessing and synthesizing the evidence, generating the evidence summaries and evidence-based draft recommendations of the Evidence Review Experts, and voting on final recommendations during the *en banc* Consensus Panel review. If any Consensus Panel member disclosed any significant competing interest, s/he was asked to abstain from votation on the pertinent recommendation.

Planning for Dissemination and Implementation

This CPG on neonatal sepsis will be useful if it positively influences the practice of the involved medical practitioners and optimizes patient care (e.g. neonatal care specialists and primary health care providers). The PSNbM and PIDSP will initiate a wide dissemination and ensure an easy access to reach all stakeholders. (See Dissemination and Implementation of the Guidelines)

The opportunity to present the CPG Recommendations for written feedback in a public forum of more than 800 participants was taken at the 5th International Convention of the PSNbM held on Jan 20-21, 2020 in Panglao, Bohol.

RESULTS

The Research Questions

A total of 11 guideline questions deemed important in current neonatal care in terms of diagnosis, screening and treatment were worded as follows:

1. *Among asymptomatic newborns delivered to mothers with maternal UTI within two weeks prior to delivery, how useful is a neonatal sepsis calculator in predicting occurrence of sepsis and all-cause mortality?*
2. *Among newborns with risk factors for neonatal infection, how accurate is each of the following CBC parameters in diagnosing sepsis? a) WBC <5000; b) WBC >30,000; c) ANC <1500; d) IT ratio>0.2; e) Plt <150,000*
3. *Among asymptomatic newborns, what is the accuracy of CBC and a single quantitative CRP in the diagnosis of sepsis?*
4. *Among newborns with clinical sepsis, how predictive of CNS infection is blood culture?*
5. *Among women near term, how effective is universal culture-based screening in preventing early onset GBS sepsis?*
6. *Among newborns with severe sepsis, how effective is double volume exchange transfusion as an adjunct in decreasing morbidity and mortality?*
7. *Among newborns with sclerema neonatorum, how effective and safe is fresh frozen plasma transfusion in decreasing morbidity and mortality?*
8. *Among asymptomatic newborns delivered meconium-stained, how effective and safe is giving antibiotic prophylaxis in preventing sepsis and all-cause mortality?*
9. *Among newborns with sepsis who improve after starting antibiotics, how effective is a shorter course (5-day) of intravenous antibiotics compared to seven days in decreasing treatment failure and mortality?*
10. *Among newborns with no risk factors for infection presenting with fever alone, what is the likelihood of them having sepsis?*
11. *Among newborns with no risk factors presenting with isolated jaundice, what is the likelihood of developing sepsis?*

The team of EREs systematically searched the scientific literature in electronic databases (MEDLINE via PubMed, CENTRAL, ClinicalTrials.gov) and local database (HERDIN) using keywords based on PICO (MeSH and free text) set for each question provided by the Steering Committee. Handsearching references of articles included were done to ensure a

comprehensive search. Authors of related articles were also contacted via email and/or phone call to identify other research studies for retrieval and appraisal.

Evidence reviewers appraised the directness and methodological validity and applicability of each relevant article included. The team constructed evidence summaries and draft recommendation for each of the 11 research questions compiled into Evidence Base (EB) Draft Recommendation on Neonatal Sepsis which was distributed to the CPG Consensus Panel prior *en banc* review (Appendix A).

The CPG Panel

A total of 13 panel members attended the *en banc* meeting on November 24, 2019 at the Hotel Benilde Maison de La Salle, Manila. The CP was composed of a nurse, an infectious disease specialist, neonatologists, a general pediatrician, a private physician, a community pediatrician, an obstetrician-gynecologist, a family physician, a government pediatrician, a hospital administrator, a public epidemiologist and two patient representatives. They voted on the critical outcomes and discussed each question, evidence summary and draft recommendations prior to generating the final recommendations.

Final Recommendations

For each guideline question, the CP members deliberated on the critical outcomes. They weighed the importance of these outcomes using a scoring system from 1 to 9: with outcomes scoring from 1 to 3 as not so important; from 4 to 6 as important; and from 7 to 9 as critical [3]. The critical outcomes for therapy questions were listed for each question in *Remarks.*

A session moderator provided a brief orientation on the nature of the question and review of quantitative measures of effect (e.g. risk ratios, odds ratios, likelihood ratios) to aid in understanding of evidence summaries. Each of the 11 pre-determined PICO questions with their corresponding evidence summary was then presented. Upon clarification and discussions, the panel voted and arrived at a recommendation. If consensus (75% of total votes) was reached before or on the third round, voting on strength of the recommendation commenced. The CP arrived at consensus in all recommendations for all 11 questions; therefore, Delphi surveys were not required.

EVIDENCE AND RECOMMENDATIONS

Sepsis Calculator in Newborns Born to Mothers with Maternal UTI

There were no studies found to directly answer the question and the specified outcomes (i.e. predicting sepsis occurrence and all-cause mortality) despite the systematic search in major databases using MeSH terms and free text. The search yielded two (2) systematic reviews and meta-analyses that looked into the comparison of the use of an EOS calculator *versus* conventional/standard management among newborns (i.e. >34 weeks age of gestation). However, these studies did not specify maternal UTI as a risk factor and used reduction of antibiotic therapy as the specified outcome. The variables (risk factors) used in deriving the multivariate model for the EOS calculator were gestational age, Group B Streptococcus (GBS) status, rupture of membranes (ROM) time, highest intrapartum temperature and intrapartum antibiotic prophylaxis.

In the first meta-analysis, Achten and colleagues reported a relative risk of antibiotic use of 52% (95% CI 53%, 59%) among newborns with the use of the EOS calculator [1]. In this meta-analysis, the proportions of missed cases of EOS were comparable between the EOS-guided group (28%) versus the conventional management strategies group (29%) (pooled OR 0.96; [95% CI 0.26, 3.52]). In the second meta-analysis, Deshmukh also demonstrated a reduction in antibiotic use among newborns > 34 weeks with an OR of 0.22 (95% CI 0.14, 0.36) in favor of EOS calculator *versus* standard management strategies [2].

Currently, there is no data to support the use of an early-onset neonatal sepsis calculator in women with UTI within two weeks of delivery to predict occurrence of sepsis and all-cause mortality. Maternal UTI as a risk factor for EOS and applicability/adaptability of an EOS calculator to our Filipino mothers and neonates are considered as research gaps.

Recommendation

No recommendation can be made at this time for the use of an early onset neonatal sepsis calculator for neonates delivered to mothers with UTI within two weeks prior to delivery.

(No recommendation. Very low quality evidence)

Remarks

A unanimous decision was made regarding not giving a recommendation because of the large research gap stemming from the absence of maternal UTI in deriving the model of an early onset neonatal sepsis calculator.

Single Abnormal CBC Parameter in Diagnosing Sepsis

Based on high level of evidence, the likelihood of sepsis in a neonate with risk factors fulfilling the category of an abnormal complete blood count is high. However, an in-depth analysis of likelihood ratios of each CBC parameter from the studies that were systematically gathered revealed using a single parameter is not helpful in diagnosing sepsis.

A series of 13 prospective and retrospective cohort cross-sectional studies done over a span of 39 years that included 4854 neonates less than 31 days old who fulfilled the criteria of an abnormal complete blood count has an overall prevalence of 10.4% (505/4854) or incidence risk of 104/1000 patients (95% CI 95.8, 112.9). The prevalence rates across all studies ranged from 0.93% to 61.4%.

Each of the parameters has low positive and negative likelihood ratios (positive LR < 3.0; negative LR > 0.3) which indicate that the likelihood of having sepsis will not change using a single CBC parameter. Moreover, across the five parameters, the PPVs in general are low. The NPVs are better across the five parameters and show that the ANC <1500 has the highest NPV. The positive and negative likelihood ratio, PPV and NPV of each of the CBC parameters are summarized in Appendix A.

Although the quality of evidence is high and there is consistency among the findings from 39 years of accumulated data, the predictive values and likelihood ratios showed that a single abnormal CBC parameter is not useful in determining sepsis among newborns with risk factors and with CBC taken at the 6th to the 24th hour of life.

Recommendation

Among newborns with risk factors, a single abnormal parameter in a CBC done within the 6th-24th hour of life should not be used alone to diagnose sepsis.

(Strong recommendation. High quality evidence)

Remarks

This recommendation was accepted unanimously. However, the panel suggested including a clinical question on combination of these parameters for the next guideline to maximize limited resources available in lower level hospitals and address possible issues of reimbursement.

Combination of CBC and A Single Quantitative CRP in Asymptomatic Newborns

Searching literature in electronic databases (e.g. MEDLINE, Clinicaltrials.gov, Cochrane database, TRIP database) using MeSH and free text methods, and hand-searching relevant published clinical practice guidelines yielded one (1) study found to directly answer the question and the specified outcome.

A cross-sectional study showed that any CRP done within three (3) days of birth in combination with WBC count showed better diagnostic accuracy in neonates with clinical suspicion of neonatal sepsis [1]. In this research, Chacha and colleagues included all neonates with clinical suspicion of neonatal sepsis according to the WHO criteria: (1) admitted at NICU and premature units. For the combination of WBC and CRP, the sensitivity, specificity, PPV and NPV were 90.3%, 50.2%, 31.6% and 95.3% respectively. Given these estimates, the positive and negative likelihood ratios (LRs) are 1.813 and 0.053, respectively.

The search also yielded two studies that looked into the diagnostic accuracy of CRP and CBC among newborns [2,3]. However, these studies included neonates with diagnosed sepsis and/ or with late-onset sepsis and qualitative determination of CRP, thus only indirectly addressing the question at hand.

The study by Beltempo and colleagues showed that among very low birth weight neonates with late-onset sepsis, the combination of CBC at T0 and qualitative CRP at T24 offered better diagnostic accuracy in neonatal sepsis [2]. For the combination of WBC at T0 and CRP at T24, the sensitivity, specificity, PPV and NPV were 88.0%, 60.0%, 46.0% and 93.0%, respectively. Using these estimates, the positive and negative likelihood ratios were 2.20 and 0.20, respectively.

The other study showed that qualitative CRP alone or in combination with WBC count resulted in a better diagnostic accuracy in neonatal sepsis. For the combination of WBC and qualitative CRP, the sensitivity, specificity, PPV and NPV were 78.5%, 83%, 60% and 93%, respectively. The positive and negative LRs were 4.618 and 0.259, respectively.

Recommendations of Other Guidelines

In well-appearing infants with risk factors for sepsis, management options include a combination of monitoring of clinical signs, abnormal laboratory parameters, blood culture determination and empiric antibiotics. The essential examinations done in a sepsis workup include a complete blood count (CBC) and blood culture and sensitivity (CS). Their results are augmented by the additional determination of concentrations of acute phase reactants, of which C-reactive protein (CRP) and procalcitonin have been the most widely studied. CRP concentration is low at birth, and may be normal during the initial stages of an infection. CRP levels may rise at least 12 hours after the onset of infection, and its sensitivity increases with serial determinations 24-48 hours after the onset of symptoms [4].Thus, CRP determination at birth or at initial presentation of infection is not recommended [5]. Most CPGs from the American Association of Pediatrics (AAP) and the National Institute for Health and Care Excellence (NICE) recommend a serial determination, as opposed to a single CRP determination, for monitoring the response to treatment and for ruling out an infection because the diagnostic accuracy of a single CRP at the time of initial investigation is poor [4, 6-7]. However, its reliability increases in the 24-48 hours after birth or after the onset of infection. At this time, a single CRP has 93% sensitivity for probable sepsis, and this increases further with a repeat determination at 48 hours [5]. These guidelines likewise stated that serial CRP in the first 48 hours was the marker of choice in the absence of clinical symptoms since it had negative predictive accuracy of 99.7% and a negative likelihood ratio of 0.15 for proven neonatal sepsis [4]. Systematic reviews and other studies on the likelihood ratios for leucocyte indexes and CRP to predict sepsis have high heterogeneity among studies to arrive at recommendations on an ideal test or combination of tests [8]

Recommendation

A combination of CBC and any single quantitative CRP is not accurate in diagnosing sepsis in asymptomatic newborns but may be more useful in ruling out sepsis when done after 24 hours of life.

(Conditional recommendation. Low quality evidence)

Remarks

This recommendation on using combination of CBC and any single quantitative CRP in ruling out sepsis when done after 24 hours of life garnered a unanimous decision among the CP members.

Blood Culture in Diagnosing CNS Infection Among Septic Newborns

Neonatal meningitis is a major concern in the NICU and early detection among high risk neonates remains a priority. Most of the studies performed lumbar puncture along with other body fluid cultures before initiating antibiotic therapy [2,3]. The studies were grouped into three based on the onset of sepsis: (1) early onset, (2) late onset and (3) those that looked at sepsis from delivery until 30 to 150 days of life.

Septicemia was defined as having a positive blood culture for a bacterial pathogen. Early-onset sepsis was defined as positive blood or CSF culture in neonates whose specimen were obtained within 72 hours of delivery while late-onset sepsis was infection occurring after the third day of delivery [1,3, 5-6]. Two studies used five (5) and seven (7) days as their cut-off for early-onset sepsis, respectively [2,9].

A. Early-Onset Sepsis

Based on five retrospective and prospective studies spanning 6 months to 7 years, only two percent (2%) of clinically septic neonates diagnosed within 72 hours with positive blood culture were positive for cerebrospinal fluid (CSF) culture [1-5]. The largest study with 5,135 symptomatic and asymptomatic term infants had an incidence of 0.6% (11/1,712) [1]. All asymptomatic neonates were negative for CSF culture. Two studies, which evaluated maternal risk factors and included 431 preterm and term infants, had a prevalence rate of 1.4% [3,4]. Overall specificity and negative predictive values were both 100% and the positive likelihood ratio (+ LR) was 9.98 (95% CI 9.08, 10.97). In this case, a positive CSF and blood culture are strongly indicative of CNS infection. The authors of this cited study believed that an early lumbar puncture may lead to false negative results and puts the infant at risk for further infection [3].

Recommendation

Among newborns with early-onset sepsis, a blood culture, when positive, is useful to predict CNS infection and should warrant lumbar puncture.

(Strong recommendation. Low quality evidence)

Remarks

A powerful positive likelihood ratio of 10 led to a strong recommendation despite the low level evidence.

B. Late-Onset Sepsis

Based on three retrospective and prospective studies spanning 1 to 3.3 years and a total of 3,141 neonatal records, the prevalence rate of CNS infection was 5% with only 3.1% (97/3,141) positive for both CSF and blood culture [1,3,6]. The negative predictive value at 96% and negative likelihood ratio at 0.78 (95% CI 0.72, 0.84), suggest that a negative blood culture result rules out a CNS infection. The sensitivity across the studies ranged from 26% to 98% (overall 62%). However, the largest study in the series was done on very low birth weight (VLBW) babies and this may have overestimated the risks, thus affecting the specificity, sensitivity and likelihood ratios [3,6]. In two of the studies, lumbar puncture was routinely done on septic neonates before initiating antibiotic therapy [1,3]. In a study, infants <7 days old were classified under EOS, possibly underestimating the rate of meningitis for LOS [1]. There was also no difference in the risk of death between septic infants with a positive and those with negative lumbar puncture at 10% each (284/2877 vs 661/6764, OR 1.01; 95% CI 0.87, 1.17) [6].

Recommendation

Among newborns with late-onset sepsis, blood culture result is not useful in predicting CNS infection. Therefore, lumbar puncture is still recommended.

(Conditional recommendation. Very low quality evidence)

Remarks

Supported by very low level of evidence, blood culture result is found to be not useful in predicting presence of neurologic infection. Themes arose in the discussion of recommending lumbar puncture for the late-onset neonatal sepsis because (1) lumbar puncture is not a standard of practice and (2) lumbar puncture is very invasive.

GBS Screening in Women Near Term

There were no randomized controlled trials found in the systematic literature search to answer this question. However, two observational studies which were included in a meta-analysis provided a very low level of evidence [1-3].

In an observational study done in Japan, only six neonates from the 710 mothers screened developed early-onset GBS disease while two newborns from the 20 unscreened mothers had

the disease [1]. The computed OR from this retrospective cohort study was 0.07 (95% CI 0.01, 0.41) indicating benefit or a decreased odds of developing early-onset GBS sepsis by 93%. However, there were no clear statements on method of culture and timing of screening among these pregnant women. In another retrospective cohort (United Kingdom), in the pre-screening period, early onset GBS rate was 0.99/1000 live births (25/25276) [2]. In the screening period, the rate was 0.33/1000 and in the subset of mothers actually screened, the rate was 0.16/1000 live births (1/6309). Despite the low point estimate (OR =0.22), there was no significant benefit suggested by a wide confidence interval with a signal of harm (95% CI 0.02, 2.44).

Based on these results, further research is needed to determine the effectiveness of universal culture-based screening among women near term in preventing early-onset GBS sepsis.

Therefore, based on the very low level of evidence and inconclusive results, universal culture-based screening among women near term is not recommended for preventing early-onset GBS sepsis.

Recommendations of Other Guidelines

In 2015, the incidence of EOGBS in United Kingdom and Ireland was 0.57/1000 births (517 cases), a significant increase from the previous surveillance undertaken in 2000 where an incidence of 0.48/1000 was recorded. Despite this increase, the Royal College of Obstetricians and Gynaecologists (RCOG) does not recommend universal bacteriologic screening of pregnant women [4].

Unlike the RCOG, The American College of Obstetrics and Gynecologists recommends performing universal GBS screening between 36 0/7 and 37 6/7 weeks of gestation. (2017) This new recommended timing for screening provides a 5-week window for valid culture results that includes births that occur up to a gestational age of at least 41 0/7 weeks. A key component of the program is targeted IV intrapartum antibiotic prophylaxis in neonates born to women with positive antepartum GBS cultures and women with other risk factors for intrapartum GBS colonization [5].

Recommendation

Universal culture-based screening of women near term should not be performed to prevent early-onset GBS disease.

(Strong recommendation. Very low quality evidence)

Remarks

The strength of the recommendation was based on the evidence presenting a low burden of disease, incidence of false positive cases related to swabbing strategies based on clinical experience, potential cost and uncertainty regarding availability of resources in our local settings.

Adjunctive Double Volume Exchange Transfusion (DVET)

Based on a high level of evidence, there was a significant decrease in the risk of mortality among septic newborns who received double volume exchange transfusion (DVET) as an adjunct to standard of care. There was a trend towards decreased risk for organ dysfunction and abnormal neurologic outcome but the findings were not significant.

A meta-analysis of six (6) RCTs including 270 neonates showed significant reduction in the risk of mortality in the DVET group compared to standard of care alone (RR 0.64, 95% CI 0.50-0.81). There was no significant heterogeneity among the included studies [1].

The RCTs included had small sample sizes (ranging between 30 and 88 neonates). Both term and preterm infants were included in the RCTs [2,3,5-7]. Only preterms were included in one RCT [4]. All studies included all infants regardless of birth weight.

Exchange transfusion was performed for all septic newborns in two trials [4,5]. Whereas, only infants with severe sepsis, as evidenced by disseminated intravascular coagulation and/or organ dysfunction were included in four clinical trials [2,3,6,7]. Subgroup analysis on the effect of DVET on all-cause mortality among infants with severe sepsis showed significant reduction in the risk of mortality in the DVET group compared to the control group (RR 0.68, 95% CI 0.52, 0.89).

The use of DVET was evaluated in five studies [2,3,5-7]. Gunes and colleagues did not specify whether single- or double-volume exchange transfusion was performed [1]. Sensitivity analysis was done to see the effect of the RCT by Gunes on the overall outcome still showed significant reduction in mortality (RR 0.66, 95% CI 0.51-0.84]) [1]. Rates of organ dysfunction by day 14 and abnormal neurologic status at the time of discharge was reported in only one study [2]. There was a trend towards decreased incidence of organ dysfunction (RR 0.78, 95% CI 0.44, 1.40) and abnormal neurologic status at the time of discharge (RR 0.51, 95% CI 0.05, 5.43) among septic neonates who received double volume exchange transfusion. However, these results were not statistically significant [2].

The reported adverse events among newborns post-DVET included intraventricular hemorrhage (2/41) [8]; mild hypothermia (36.0 – 36.4 °C) during line placement for DVET (12/41); transient bradycardia that spontaneously recovered (2/41); serum potassium >6.5 mEq/L without any electrocardiography evidence (2/41); and serum sodium >145 mEq/L which resolved spontaneously (2/41) [2].

Significantly lesser neonates in the DVET group had progression of thrombocytopenia with an (RR 0.48, 95% CI 0.30, 0.76); and worsening of metabolic acidosis (RR 0.26, 95% CI 0.08, 0.84) following DVET [2].

Table 3. Summary of Results

OUTCOMES	Measure of treatment effect	95% CI	Interpretation	Basis
All-cause mortality	0.64	0.50-0.81	Significant	6 RCTs
Organ dysfunction by day 14	0.78	0.44-1.40	Not significant	1 RCT
Abnormal neurological status at time of discharge	0.51	0.05-5.43	Not significant	1 RCT
Progression of thrombocytopenia	0.48	0.30-0.76	Significant	1 RCT
Worsening metabolic acidosis	0.26	0.08-0.84	Significant	1 RCT

The result of the meta-analysis on the outcome of all-cause mortality was driven mainly by the four RCTs done from years 1971-1997 [3,5-7]. They showed dramatic differences in treatment effect which may have been due to limited modalities of treatment for sepsis during this period. This is evidenced by the high control event rates in these RCTs (Gross 3/11, Mathur 7/10,

Narayanan 18/20, Sadana 19/20) [3, 5-7]. Subgroup analysis of these 4 RCTs showed significant reduction in all-cause mortality in the DVET group RR 0.62 [95% CI 0.47, 0.82]. Whereas, subgroup analysis of the two more recent RCTs [2,4] showed a trend towards decreased mortality but the result was not significant (RR 0.67, 95% CI 0.43-1.05). This result may be due to the low control event rates in the latter studies (Gunes 9/22, Aradhya 19/42) [2,4].

The RCTs in this review included infants admitted in neonatal intensive care units of tertiary referral centers capable of providing high level of neonatal care. As such, the results should be applied to similar populations only. Caution must be exercised in the applicability of these results in other populations.

Recommendation

Among newborns with severe sepsis, double volume exchange transfusion as an adjunct treatment is recommended.

(Conditional recommendation. High quality evidence)

Remarks

The consensus panel selected mortality, organ dysfunction by day 14 and abnormal neurological by the time of discharge as outcomes critical to formulating this recommendation. The panel also suggested to include subgroup analysis separating the older studies from the more recent studies. This analysis still showed a lower risk of harm (RR 0.59, 95% CI 0.43, 0.92). In spite of high level evidence and a trend towards benefit, consensus issues arose as to whether to recommend DVET due to lack of local studies and uncertainty in terms of timing of administration (i.e. early or late) and the type of provider present in areas far from a tertiary referral center (i.e. primary care provider or specialist) capable of administering the adjunctive treatment. Supported by evidence, DVET as an add-on treatment is recommended in tertiary hospitals with adequate resources (e.g. experienced practitioners and available equipment) in NICUs providing high levels of neonatal care.

Fresh Frozen Plasma in Sclerema Neonatorum

The overall quality of the evidence was downgraded due to indirectness being that the included participants were those who were very preterm. The literature search in the different databases did not yield studies specific to the effectiveness of fresh frozen plasma (FFP) in decreasing

morbidity and mortality among newborns with sclerema. The participants in the trials included, received early treatment (fresh frozen plasma within the first 24 hours of life).

The trials reported adequate randomization procedures and allocation concealment. However, despite the nature of the intervention, none reported efforts to blind caregivers. Given the nature of the intervention, it is unlikely this was possible. Only one trial provided data on long term neurodevelopment [1]. This was the largest trial with no losses to follow up; blinded assessment of neurodevelopment was done at two years. Another possible limitation of the trials would be the time period that they were conducted, thus, potentially limiting the significance of its results to current neonatal practice.

The meta-analysis examined the potential role of early volume expansion for the prevention of morbidity and mortality in very preterm infants [2]. In the subgroup analyses, four studies randomized infants to fresh frozen plasma or no treatment with volume expanders. Meta-analysis of three studies reporting mortality data involving a total of 654 infants found no significant difference in mortality (RR 1.05; 95% CI 0.81, 1.36) [1,3-4]. Furthermore, the rates of severe disability (RR 0.80; 95% CI 0.48, 1.34), death or severe disability (RR 0.94; 95% CI 0.73, 1.22) and cerebral palsy (RR 0.79; 95% CI 0.46, 1.34) were not significantly different but with signals of harm.

Beverley and co-researchers reported a significant reduction in periventricular/intraventricular hemorrhage (P/IVH) [3]. In contrast with the findings of Ekblad, there was no found significant difference. Meta-analysis of these two studies found a non-significant trend to reduced P/IVH in infants receiving FFP [5]. Among the survivors examined, a group of researchers also reported no difference in the reduction of P/IVH [4]. There was also found no significant difference in patent ductus arteriosus (PDA) in a meta-analysis of two studies [4,5].The results of the studies also show no significant difference in the rates of pneumothorax.

In summary, the overall rate of mortality and disability were not different between infants who received FFP compared to no “volume expanders.” With the limited evidence available to inform the use of FFP transfusion among neonates with sclerema, it is difficult to make definitive recommendations. Currently, there is no supporting evidence to recommend its use.

Recommendation

The use of fresh frozen plasma among newborns with sclerema neonatorum in order to decrease morbidity and mortality is not recommended.

(Strong recommendation. Low quality evidence)

Remarks

The panel voted mortality as the only critical outcome. The signal of harm warranted a strong recommendation to not use FFP transfusion among newborns with sclerema neonatorum. Indirectness and inconclusiveness of the evidence imply a need for further research.

Antibiotic Prophylaxis in Asymptomatic Newborns Delivered Meconium-Stained

A meta-analysis of four (4) RCTs evaluated the effectiveness of antibiotics in reducing infection among 695 full-term infants born as singleton cephalic presentation through meconium-stained amniotic fluid [1]. Primary outcome of the trials was culture-proven (confirmed) sepsis. There was a low risk for bias because selection, performance, attrition, and reporting biases were all well-accounted for. One of the limitations would be the fact that all four trials compared antibiotics versus no treatment and did not include a placebo control which may have resulted in biased reporting. Another limitation was the lack of full blinding of attending clinicians. Moreover, there was an overall low event rate for sepsis in both the intervention and control arms of the trial. Therefore, the evidence was downgraded due to serious imprecision related to a small sample size and the unclear risk of bias in outcome assessment.

No difference was identified in risk of infection (confirmed sepsis) among neonates receiving antibiotics and controls following meconium exposure. All four included trials consistently reported no significant improvement in infection reduction with antibiotic treatment or prophylaxis despite use of different antibiotics and treatment durations.

Only one RCT in the meta-analysis contributed data for the comparison of antibiotics versus control (no treatment with antibiotics) in asymptomatic neonates [2]. There was no evidence that antibiotics significantly decreased the risk of sepsis in asymptomatic neonates exposed to meconium in amniotic fluid (RR 0.76; 95% CI 0.25, 2.34). Results also showed no significant difference in mortality between the group given antibiotic and the control group of asymptomatic neonates (RR 1.07; 95% CI 0.22, 5.18).

For the morbidity outcomes, suspected sepsis was confirmed in 50% of all cases in both the antibiotic and control groups. Results showed no significant difference in the incidence of suspected sepsis between groups. Furthermore, results also showed no statistically significant

differences in the incidence of intracranial hemorrhage, azotemia, oliguria, diarrhea and respiratory distress between groups.

The studies included in the meta-analysis did not provide data on the cost of antibiotic prophylaxis for newborns delivered meconium-stained. Moreover, only one study reported the outcome of "duration of hospital stay until discharge among survivors (days). In a study, it was noted that no statistically significant differences in the mean duration of hospital stay between neonates who received antibiotics and those in the control group (mean difference 0.16; 95% CI -1.15, 1.47; 146 participants) [3]. However, this outcome was only reported among symptomatic newborns.

Based on the available low quality evidence, there is no difference in the risk of sepsis following antibiotic treatment among asymptomatic neonates born through meconium stained amniotic fluid. There is a need to generate more studies on the efficacy and cost-effectiveness of antibiotics as prophylaxis among asymptomatic term newborns delivered meconium stained, before recommending antibiotic prophylaxis in routine clinical practice.

Table 4. Summary of Results

Outcomes	Measurement of Treatment Effect	95% Confidence Interval	Interpretation	Basis
Incidence of confirmed sepsis in first 28 days of life	RR 0.76	0.25-2.34	Not significant	1 RCT
Mortality before discharge	RR 1.07	0.22-5.18	Not significant	1 RCT
Incidence of suspected sepsis	RR 0.76	0.35-1.65	Not significant	1 RCT
Incidence of intracranial hemorrhage	RR 0.36	0.01-8.64	Not significant	1 RCT
Incidence of azotemia	RR 3.20	0.13-77.73	Not significant	1 RCT
Incidence of diarrhea	RR 0.12	0.01-2.18	Not significant	1 RCT
Incidence of respiratory distress	RR 1.18	0.81-1.72	Not significant	1 RCT

Recommendation

Antibiotic prophylaxis for asymptomatic newborns delivered meconium stained is not recommended.

(Strong recommendation. Low quality evidence)

Remarks

The critical outcomes considered by the panel members were incidence of confirmed sepsis in the first 28 days of life, mortality before discharge, suspected sepsis, intracranial haemorrhage, respiratory distress and azotemia. A consensus was made with regard to a strong recommendation despite low level of evidence because of the observed rampant use of unnecessary antibiotics in neonates, which may cause harm. Meconium passing in utero does not equate to the fetus having an infection; therefore, antibiotic therapy is not necessarily indicated in the newborn. In addition, shorter hospital stay and consequent lower cost were important to the CP patient representative. The strong recommendation called for promoting antibiotic stewardship among medical professionals.

Duration of Antibiotics in Septic Neonates Who Improve After Starting Antibiotics

Treatment failure is defined *a priori* as recurrence of symptoms after completing a certain duration of intravenous antibiotics.

There were no studies available comparing the original antibiotic duration (E) from the question despite the systematic search of major electronic databases (MEDLINE via Pubmed, CENTRAL, ClinicalTrials.gov) and hand-search of 22 articles. There were also no studies available in local databases included in this search. However, three randomized controlled trials were deemed indirect but relevant to our clinical question, thus, were used as available evidence.

These randomized controlled trials were done in low-income countries [1-3]. All studies included newborns in neonatal intensive care units with probable sepsis or those with clinical signs of sepsis but had negative results of blood culture after having empirical intravenous antibiotics. In one study, authors included infants with birth weight over 1500g, gestational age over 34 weeks and were observed within 7 days postnatal age [1]. These infants were randomized after 72 hours of being asymptomatic. Investigators in Iran compared 3-day and 5-day IV antibiotics in terms of preventing treatment failure. In the second RCT, newborns included were those with more than 1000g and with gestational age of more than 30 weeks [2]. They also started antibiotics for probable sepsis supported by a positive C-reactive protein (CRP) test. The infants randomized in the short-course group (between 48 hours to 96 hours) did not receive antibiotics after having negative blood culture results. The control group received 7 days of antibiotics. Outcome in both studies was treatment failure defined as reappearance of signs and symptoms of neonatal sepsis diagnosed by an expert physician and

supported by laboratory findings [2,3]. This outcome was observed within two weeks (14-15 days) [2,3]. In addition, mortality was not mentioned as the primary outcome but was reported in the study results (Table 5). The last clinical trial included in this review was still indirect in terms of intervention (3-day and 7-day antibiotics). Neonates with probable sepsis identified based on clinical signs of sepsis and positive septic screen and who were on antibiotic therapy and had sterile blood culture at the third day of admission were observed in NICU. The investigators determined outcomes such as successful therapeutic outcome including absence of apparent signs of sepsis ascertained by clinical examination and absence of rehospitalization caused by sepsis. Mortality was not reported as outcome in this trial.

The study analysing the effects of shorter course versus 7-day IV antibiotics has lower risk of bias than the other RCT investigating similar duration. However, combining these studies still result to very serious methodological limitations. One study comparing the two shorter courses of intervention also has poor methodological quality.

Table 5. Summary of results

Outcomes	Measure of Treatment Effect	95% Confidence Interval	Interpretation	Basis
Treatment failure (3 days vs 7 days)	RR 0.14	0.01 - 2.63	Not significant	2 RCTs
Treatment failure (3 days vs 5 days)	RR 3.00	0.13 - 70.83	Not significant	1 RCT
Mortality (3 days vs 7 days)	RR 0.33	0.01- 7.81	Not significant	1 RCT

Although the point estimate shows 86% reduction in treatment failure with the shorter course, the confidence interval is wide with the worst case scenario raising a signal of harm (Table 5). It means that those who receive a 3-day intervention can be three times as likely to be at risk of having treatment failure as those who receive a 7-day IV antibiotics. Similarly, there is no sufficient evidence to say that there is a decrease by 67% in the risk of mortality among newborns who receive IV antibiotics in an average of 3 days [1]. The shorter course when compared with a five-day intervention can also be harmful but it also has reported 87% reduction in the risk of treatment failure [1]. This study has poor methodological quality aside

from its inconclusive results. There were no reported cases of neonatal deaths in the two groups of treatment regimen [1].

Given these indirect and inconclusive findings, the available evidence is not adequate to determine the effectiveness of a shorter course of intravenous antibiotics compared with a 7-day course among newborns with sepsis who improve after starting antibiotics. However, this current available evidence on the shorter course of antibiotics among these newborns still showed an apparent risk of harm.

Recommendations of Other Guidelines

In United Kingdom, the usual length of antibiotic treatment for newborns with a positive blood culture and for those with strong suspicion of sepsis even with a negative blood culture is 7 days [4]. Similarly, WHO supported the Integrated Management of Childhood Illness (IMCI) which recommends that IV antibiotics should be at least 7-10 days in infants aged less than two months with serious bacterial infection [7]. In US, AAP recommended when blood cultures are sterile, antibiotics should be stopped by 36 to 48 hours of incubation unless there is proven infection on a specific site for neonates born ≥35 weeks' and <34 weeks' gestation [5,6]. However, persistently unstable cardiopulmonary status is not unusual among premature infants with VLBW; it is not the sole indication for prolonged empirical antibiotic therapy [6]. Moreover, using abnormal laboratory tests only cannot always justify prolonged antibiotics, particularly among preterm infants with lower risk for early-onset sepsis (e.g. those with maternal delivery conditions affecting hematopoiesis) [6].

Recommendation

A 5-day course over a 7-day course of intravenous antibiotic is not recommended for newborns with clinical sepsis who improve after initial antibiotic therapy.

(Strong recommendation. Low to very low quality evidence)

Remarks

The outcomes critical in not recommending the 5-day course were treatment failure and mortality. Discussions revolved around the definition of clinical sepsis which warranted a strong recommendation for a low to very low level of evidence. Newborns exhibiting clinical signs and symptoms of sepsis supported with abnormal laboratory findings is recommended to continue the 7-day IV antibiotics because aside from the increased risk of harm, it is also endorsed by international guidelines (e.g. NICE and WHO). Moreover, panelists consider the additional

burden including cost of re-hospitalization caused by possible treatment failure that was presented in the evidence summary.

Presence of Fever Alone in Determining Likelihood of Sepsis

Based on low to moderate level of evidence, the likelihood of sepsis in an otherwise healthy-looking infant who presented with isolated fever was low, especially when the neonate was: 1) previously healthy with no prenatal or natal antibiotic treatment; 2) no chronic illness; 3) born term; 4) did not have any evidence of skin, bone, joint, or ear infection, and; 5) laboratory values and blood culture were normal [1,3,4].

Seven prospective and retrospective cohort studies over a span of 1.5 to 10 years included 1,894 neonates less than 31 days old who presented to the emergency room with a rectal temperature of ≥38°C. The standard laboratory screening tests for sepsis included white blood cell count (WBC), absolute neutrophil count (ANC), quantitative C-reactive protein determination, urine analysis and culture of blood, CSF, urine and other body fluids. Sepsis was considered present if the WBC <5000/mm or >15000/mm and/or ANC >10000/mm and /or CRP >20mg/L and/or positive urinalysis [2, 5-7].Systemic bacterial infection (SBI) was defined when a bacterial pathogen was isolated from a culture of the CSF, blood, urine, joint fluid, stool, pus or other body fluid [1,3-7].Three studies included radiographic studies in their criteria for SBI [2,6-7]. These cohort studies reported an overall prevalence of sepsis of 20% (374/1894), 95%CI 18-22%. The prevalence rates across all studies were almost similar, ranging from 12.6% to 25.3%.

Only one study specifically used blood culture to diagnose sepsis among the infants [1]. This 36-month consecutive cohort (Pennsylvania) included 254 febrile, 3-to-28-day old neonates who presented to the ER with rectal temperatures of 38°C. Of the 254 febrile neonates, 109 (42.9%) were identified as at low risk for SBI. Of these 109, five low-risk neonates (4.6%) had bacterial diseases while the 104 (95.4%) had either a viral syndrome (n=87), gastroenteritis (n=14), bronchiolitis (n=1) and viral encephalitis (n=2). Thirty-two neonates out of those 254 (12.6%) had SBI (27 were positive for the screening test and 5 low-risk infants). The remaining 222 neonates (87.4%) were culture-negative. The study identified five low-risk neonates who turned out to be culture-positive, hence, the recommendation to do a complete evaluation with empirical antibiotic treatment [1].

Six studies had almost similar protocols, which assessed the reliability and usefulness of the low risk criteria (LRC) in identifying the febrile neonates unlikely to have sepsis. LRC was

based on the parameters mentioned above plus laboratory findings such as normal WBC (5,000-15,000 with < 1,500 bands), ESR <30mm/hr, urinalysis with < 1 WBC/hpf, CRP <20mg/L, and normal stools (if no pus cells). Sepsis was generally defined as having a bacterial pathogen isolated from culture of CSF, blood, urine, joint, stool or other body fluids with ≥105 colonies/ml of a single pathogen.

The studies ranged from 1.5 years to 10 years of accumulated data on 1,640 neonates. The prevalence rate or pre-test probability was 21% (344/1,640) ranging from 16.4% to 25.3%. The studies showed similar findings regarding the accuracy of the LRC in the febrile neonates only. No local studies were found to add on evidence.

While the quality of the available evidence is low given that most of these were observational and not controlled, there is consistency among the findings from 17 years of accumulated data. The variability lies in the modified low risk criteria and laboratories performed on the neonates and the concomitant action done at the emergency room during the initial presentation of the febrile infant. Given these findings, an otherwise healthy neonate presenting with isolated fever and fulfilling the low risk criteria (LRC) has a 20% chance of developing sepsis.

Recommendation

Recommendation was not possible.

(No recommendation. Low quality evidence)

Remarks

The panel cannot make a recommendation in using isolated fever in diagnosing sepsis among newborns with no risk factors for sepsis because the nature of the question does not entail a clinical action. Moreover, there is no available evidence that provides a direct answer to the guideline question at hand.

Presence of Jaundice Alone in Determining Likelihood of Sepsis

Based on low level of evidence, the likelihood of developing sepsis in an otherwise healthy-looking newborns presenting with isolated jaundice is low, especially when the neonate: 1) has no other risk factors for developing sepsis, 2) has negative blood culture results, 3) has negative urine cultures or 4) has negative CSF cultures.

A series of five studies (two prospective, two retrospective cohort studies and a case-series) included 774 neonates presenting with jaundice with 122 healthy patients as controls [1-5]. Neonates less than 31 days old who were admitted to the ICU and readmissions presented

with jaundice with no other risk factors nor other presenting signs and symptoms, but with positive blood culture, urine culture and CSF studies. The overall prevalence rate of jaundice proven by culture studies was 57.60% (516 jaundiced out of 896 total patients included in the studies) with an odds ratio of 27.65 (95% CI 3.77, 202.76). The prevalence rate of developing sepsis is 3.9% (35 true positives/896 total patients).

Investigators in three studies used blood, urine and CSF cultures [1-3]. On the other hand, either blood and urine culture only or urine cultures alone in the remaining two studies [4,5]. The case series yielded a prevalence rate of 80% (4/5) from the urine culture [4].

Records review and observations were used in all the three older studies in analyzing the patient's characteristics and factors while a comparison of two groups of healthy-looking neonates in terms of presence of UTI in more recent studies to determine the diagnosis of jaundice [1-5]. There were no deaths reported in the studies. Antibiotics were given to those who had positive urine and blood cultures, and who presented with symptoms. Notably, UTI was the most common infection associated with idiopathic jaundice.

While the quality of evidence is low given that most of the studies were observational and not controlled, there is consistency among the findings from 45 years of accumulated data. Thus given these findings, an otherwise healthy neonate presenting with isolated jaundice has 3.9% probability of developing sepsis.

Recommendation

Recommendation was not possible.

(No recommendation. Low quality evidence)

Remarks

The panel cannot make a recommendation in using isolated jaundice in diagnosing sepsis among newborns with no risk factors for sepsis but they provided insights because this question is significant in the current medical practice. First, this guideline question was considered as a background question that does not entail a clinical action. Moreover, there is no available evidence that provides a direct answer to this guideline query. Second, the panel members considered this question as a research gap that needs to be filled in, especially in the local context. Lastly, this question on isolated jaundice should be prioritized in the next or other related guidelines.

RESEARCH IMPLICATIONS

The CPG Task Force 2019 identified important gaps in knowledge that need to be addressed through further research to provide clear and specific evidence significant in formulating recommendations for the next practice guidelines on neonatal sepsis.

These gaps surfaced with evidence of low to very low quality: early-onset neonatal sepsis calculator; blood culture in predicting CNS infection among newborns with late-onset sepsis; universal GBS screening; fresh frozen plasma transfusion; antibiotic prophylaxis among newborns born meconium-stained; and duration of antibiotics (5-day vs 7-day course) among septic neonates who improve after starting antibiotics.

The panel gave a strong recommendation to not perform the three treatments (FFP transfusion, antibiotic prophylaxis for asymptomatic meconium staining of amniotic fluid and shorter course of antibiotic therapy) despite the low quality evidence due to high risk of harm. Outcomes such as length of hospital stay, re-hospitalization and its cost must be addressed in future research on said treatments.

Other important research gaps were highlighted in DVET as an adjunctive therapy. The paucity of local data has resulted in significant equity issues because of probable limited number of specialists to perform the procedure and inaccessibility of this adjunctive treatment in those remote areas in the country where disadvantaged groups are residing. Moreover, the timing to provide this add-on therapy is also still uncertain in the current evidence.

DISSEMINATION AND IMPLEMENTATION OF THE GUIDELINES

Dissemination to the Members

This CPG was presented to the PSNbM members at their Annual Business Meeting on Jan 20, 2020 and to participants of the 2020 PSNbM Annual Convention on Jan 21, 2020. It will be presented at the 2020 PIDSP Annual Convention. A full copy of this document will be published online in the PSNbM and PIDSP websites aside from the printed copies that will be made available in mentioned societies.

Dissemination to the Training Institutions

The Neonatal Sepsis Task Force requested the Boards of Examiners of the PSNbM and PIDSP to endorse this CPG. Copies of the CPG with the PSNbM and PIDSP endorsements will be sent to medical schools and libraries so as to incorporate the recommendations in their teaching and training curricula, with the support of the consultants and mentors, heads of hospital-based departments of pediatrics, sections of newborn medicine, training institutions and birthing centers, the Association of Philippine Medical Colleges Foundation, Inc., and the Board of Medicine of the Professional Regulations Commission.

Dissemination to Industry Partners, Regulatory Agencies and Payors

The Disease Prevention and Control Bureau of the Department of Health will transmit copies of this CPG to the Philippine Health Insurance Corporation (PHIC), health maintenance organizations (HMOs), NGOs involved in maternal and newborn health, and pharmaceutical industry partners.

Dissemination to Patients and the Public in General

The Neonatal Sepsis Taskforce plans to develop a simplified or 'laymanized' version of the CPG to be made available to the PSNbM and PIDSP members in a format that will be ready for reproduction and dissemination to their patients in their clinics and hospitals. The same will be available for interested parties who might browse the PSNbM and PIDSP website.

Implementation and Monitoring

The Neonatal Sepsis Taskforce will distribute a questionnaire annually for the purpose of determining the preferred practices of PSNbM and PIDSP members with regard to screening, diagnosis, treatment and prevention of neonatal sepsis and clinical dilemma that persist. The results shall be compiled and tracked annually to monitor adherence of practice patterns with the CPG recommendations and guide updating of CPGs.

APPLICABILITY ISSUES

The Neonatal Sepsis Task Force, using equity and applicability lenses, flagged some caveats here reemphasized:

This CPG does not supplant existing protocols for the timing of workup for neonatal sepsis, choice of empirical antibiotics, shifting of antibiotics etc. Comprehensive history taking, thorough physical examination and conscientious monitoring of a newborn's vital signs, overall

activity and physical stability are essential to the evaluation of their sepsis status and response to therapy.

Though the expertise in care of the high risk neonate may not yet be widely distributed across all the regions of the country, an increase in the capacity and improvement in accessibility to neonatology centers is in the pipeline, with more neonatologists being trained and deployed to regional referral centers.

UPDATING OF THE GUIDELINES

The recommendations herein shall hold until such time that new evidence on interventions for neonatal sepsis and/or patient and provider preferences require, or contingencies dictate the revision and updating of practice guidelines.

The Neonatal Sepsis Task Force plans to review this CPG no later than 2022.

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