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Current Evidence on Prevention and Management of Early Onset Neonatal Sepsis

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Introduction

Early onset neonatal sepsis (EONS) continues to be a challenge in modern neonatal care and is fraught with many diagnostic and management conundrums. In a large single centre report the incidence of sepsis in intramural babies was 0.7% and the reported mortality due to sepsis/meningitis was 4.1% [1]. Institutional protocols vary in the various aspects of antenatal and postnatal care. Identifying neonates at risk for EONS by maternal risk factor assessment or maternal screening, intrapartum antibiotic prophylaxis and other maternal interventions for reducing the incidence, ideal haematological parameters, acute phase reactants and sepsis screen for at risk neonates, improving the blood culture yield, lumbar puncture for cerebrospinal fluid (CSF) examination, selection of antibiotic, duration of therapy and role of intravenous immunoglobulin are some of the questions which plague the clinician.

Prevention of Early Onset Neonatal Sepsis

Intrapartum antibiotic prophylaxis

Intrapartum antibiotic prophylaxis (IAP) has been recommended for use in mothers in order to reduce the incidence of EONS [2]. It is the only intervention which has been shown to reduce the incidence of EONS in group B streptococcal infection [3]. In a study on 600 mother-infant dyads from the Indian subcontinent intrapartum antibiotics appeared to be protective (OR 0.381, 95% CI 0.115–1.258). However, the confidence intervals were very wide and after adjusting for prematurity, wealth status, and maternal colonization status (OR 0.361, 95% CI 0.106-1.225) there was no difference in the results [4]. A multicentric case-control study on EONS in neonates found that in 49% cases of GBS sepsis and 79% cases of sepsis due to other organisms, maternal risk factors like spontaneous preterm onset of labour (SPTOL), intrapartum fever and prolonged rupture of membranes for >18 hours (PROM) were present. Preterm birth correlated lesser with GBS sepsis than sepsis due to non-GBS organisms. In comparison to healthy matched controls EONS due to GBS was associated with intrapartum fever (matched OR 4.1; CI 1.2 ± 13.4) and frequent vaginal exams (matched OR 2.9; CI 1.1 ± 8.0). The study reported a very high efficacy of 68.2% of intrapartum antibiotic prophylaxis against EONS whether due to GBS or due to non-GBS organisms [5]. Another large prospective cohort study showed that many well recognized risk factors for EONS such as PROM, SPTOL, preterm premature rupture of membranes (pPROM) do not remain significant when a policy of IAP is instituted. It went on to identify independent risk factors for EONS such as clinical chorioamnionitis, repeated per vaginal examinations, male sex, birth weight<1500 grams, gestation<30 weeks and non-exposure to IAP [6]. Institution of antibiotic prophylaxis may be 'intrapartum' or 'postnatal' based on screening of mothers for bacterial colonization or infection or evaluating them based on risk factors during pregnancy which increase the risk of EONS. Both these strategies are highly effective in reducing EONS in developed countries. However screening based approach is less likely to be beneficial in developing countries where a risk-factor based approach is more applicable [7]. In another study mothers with confirmed infection and those with colonization had very high odds of delivering a baby with lab-confirmed EONS (OR 6.6, 95% CI 3.9-11.2) as compared to mothers who were not colonized (OR 9.4, 95% CI 3.1-28.5). In these mothers, risk factors like pPROM and PROM resulted in a much higher odds of infection than mothers without risk factors (OR 2.3, 95% CI 1.0-5.4) (Table 1) [8].

Clean delivery practices

Studies from the Indian subcontinent on clean delivery practices and use of clean delivery kit was associated with a relative reduction in neonatal mortality (adjusted OR 0.52, 95% CI 0.39–0.68). While use of a clean delivery kit was not always accompanied by clean delivery practices, using a plastic sheet during delivery, a boiled blade to cut the cord, a boiled thread to tie the cord and antiseptic to clean the umbilicus were each significantly associated with relative reductions in mortality independent of kit use. Each additional clean delivery practice used was associated with a 16% relative reduction in neonatal mortality (OR 0.84, 95% CI 0.77–0.92) [9]. A systematic review and meta-analysis on clean birth practices showed poor quality evidence supporting clean birth and postnatal care practices to have an impact on neonatal sepsis and tetanus. The authors undertook a Delphi expert opinion and reported a reduction in neonatal sepsis deaths by clean birth practices at home by 15% (IQR 10-20), at a facility by 27% (IQR 24-36) and by clean postnatal care practices 40% (IQR 30-50) [10].

Maternal immunization and antenatal steroids

Immunisation of expectant mothers is an important population strategy for providing the unborn fetus and the neonate with protective antibodies. Immunization with tetanus toxoid and influenza has been successfully applied in this population. Studies on maternal immunisation with Streptococcus agalactiae type III conjugate vaccine have shown excellent fetal and neonatal protection.

Action	Recommendation	Level of evidence/ Quality for the recommendation	Type of Studies
Screening of mothers for infection or carriage	Recommended, however, is less likely to be beneficial in developing countries where a risk-factor based approach is more applicable	IIb/High quality	Review article & Population based surveillance studies [7]
Assessing mothers for risk factors for EONS	Recommended	Ia/High quality	Systematic review and meta-analysis [8]
Maternal Immunization using PCV	Not recommended	Not enough evidence	Review [11]
Intrapartum antibiotic prophylaxis	Recommended, the only intervention which has been shown to reduce the incidence of neonatal sepsis	IIb/High quality	Historical cohort study [2] Guidelines [3] Prospective cohort study [4] Case-control study and multicentre surveillance data [5] Prospective cohort study [6]
Clean delivery practices	Recommended, each additional clean delivery practice was associated with a 16% reduction in mortality	Ia/High quality	Cluster-RCT's [9] Systematic review and meta-analysis [10]
Hematological parameters	WBC<5000, ANC<1500 and IT ratio done within 4 hours age are highly predictive. CBC is useful with increasing postnatal age and when interval likelihood ratios are used rather than a 'normal value'.	IIb/Moderate quality	Retrospective cross-sectional study [13] Review [15]
Acute phase reactants: CRP and PCT	Single CRP lacks sensitivity and specificity. Serial CRP estimations are useful. Combination models are highly specific (96-100%). Two negative CRP values have a negative predictive value of 99.7%. PCT estimation has sensitivity of 88% but is confounded by non-infectious causes of elevated levels and different cut-offs w.r.t postnatal age.	Ia/High quality	Review [14] Prospective study [16] Systematic review and meta-analysis [17]
Sepsis screens	A sepsis screen with micro ESR, I/T ratio, PBS for neutrophil changes and CRP has a high specificity of 95-100%. A combination of PCT,CRP and IL-6 showed a sensitivity of 82-88%.	IIb/Moderate quality	Observational study [18] Prospective study [19]
Blood culture	At least 1 ml blood added to the blood culture (in an automated culture system) will double the yield compared to 0.5 ml	IIb/Moderate quality	Guidelines [3] Observational study [22]
Empirical antibiotic therapy	Prophylaxis is recommended in all preterm neonates<34 weeks born to mothers with risk factors for EONS. In well appearing newborns including preterm>34 weeks with risk factors for EONS, clinical monitoring and a sepsis screen should be used to decide initiation of antibiotics within 6 hours.	1b/High quality	RCT [23] Review [24] Population based study [25] Systematic review [26] Observational study [32]
Antibiotic selection	Empirical antibiotic therapy should be individualized for each hospital or region	1b/Moderate quality	RCT [23] RCT [27]
Duration of therapy	Blood culture positive EONS requires antibiotic for 10-14 days. Gram negative meningitis for 21 days or 14 from a negative blood culture. In culture negative EONS, the clinical features vs risks of a longer course (death, NEC) need to be considered.	1b/Moderate quality	Guideline [3] Review [28] Review [30] RCT [31]
IVIG administration	Studies evaluated role in preterm and LBW for preventing sepsis. Modest 3% reduction in sepsis noted. However, no mortality benefit. Maybe used depending on availability and resources at disposal.	Ia/High quality	Systematic review & meta-analysis [33]

Table 1: Recommendations for Prevention and management of early onset neonatal sepsis with the Level of evidence and the Quality for the recommendation of the studies.

Studies of maternal immunisation with pneumococcal polysaccharide and conjugate vaccines have shown encouraging results [11]. Antenatal steroids are strongly recommended because their use results in a reduction in systemic infections in the first 48 hours of life compared to not using them in the antenatal period [12].

Diagnosis of Early Onset Neonatal Sepsis

Hematological indices, acute phase reactants and sepsis screen

For diagnosis of EONS no single test in isolation has sufficient sensitivity or specificity. In a large study of neonates >34 week gestation, >67000 complete blood counts (CBC) and blood culture pairs were taken in the first 72 hour of life. Of these there were 245 blood-culture positive cases. The study highlighted the fact that instead of using cut-off values for "normal or abnormal", the use of interval likelihood ratios was superior at identifying an abnormal count. If the total WBC, ANC and I/T ratio was measured after 1-4 hours of life improving likelihood ratios were observed. The WBC and the ANC predicted an infection when these values were low (WBC<5000; ANC<1000 per cu.mm) while an elevated WBC (>20000 per cu.mm) was not useful. The I/T ratio was the most informative if measured at <4 hours of life; low values (<0.15) were reassuring while elevated values (>0.30) were associated with EOS [13]. Amongst the acute phase reactants serial CRP estimation is used to identify probable EOS and guide length of antibiotic treatment for symptomatic infants with culture negative clinical sepsis. CRP levels increase 6 to 8 hours after the onset of infection and may increase more than a 1000 fold as an acute phase reactant. Thus CRP has been aptly describes as a late but specific marker [14]. It is for this reason that a single estimation of CRP at birth has very poor sensitivity and specificity for EOS. The best predictive ability of CRP for EONS lies when it is measured with in 24 to 48 hours of birth or a rising CRP level is seen. Two normal CRP determinations (8 to 24 hours after birth and 24 h later) have been shown to have a negative predictive value of 99.7% and a negative likelihood ratio of 0.15 for proven neonatal sepsis [15]. Multiple normal CRP results strongly argue against the presence of bacterial sepsis enabling us to stop antibiotics. Procalcitonin (PCT) is a pro-peptide of calcitonin secreted by the monocytes and hepatocytes. It is more likely to be elevated in EONS compared to CRP. However, there is a physiologic elevation of PCT seen in the first 24 hours and non-infectious conditions such as respiratory distress syndrome (RDS) and birth asphyxia can result in elevated levels. PCT thresholds for diagnosis of sepsis at birth are 0.55 ng/ml at birth, 4.7 ng/ml at 12-24 hours and 1.7 ng/ml by 36-48 hours age [16]. A meta-analysis of six studies evaluating the predictive ability of PCT to identify early onset culture-positive sepsis or clinical sepsis found the pooled sensitivity and specificity of PCT to be 76% with sensitivity improving after 24 hours of age [17]. A sepsis screen with micro ESR, I/T ratio, neutrophil morphological changes on a peripheral blood smear and CRP is useful for diagnosis of EONS with a combination of three or all of these four tests having a high specificity of 95–100% [18]. PCT with CRP and IL-6 has been studied as a sepsis screen for EONS. The study revealed a sensitivity of 88% with PCT and IL-6 and 82% with PCT and CRP [19]. Cytokines like IL-6, IL-8, IL-10, IL-1β, G-CSF, TNF-alpha and CD64 have shown correlation with culture-positive or probable sepsis. None of them are validated as independent screening tool for EONS risk assessment [20].

Blood culture

The volume of blood for blood culture in neonates is much lesser as neonates have 1-log-higher concentration of bacteria in their blood. Also about one quarter of all neonates with sepsis have low level bacteremia with low colony counts (≤ 4 CFU/ml) [21]. Thus, single blood culture with 1 ml of blood added will double the yield of bacterial isolation compared to 0.5 ml of blood [22].

Management of Early Onset Neonatal Sepsis

Empirical antibiotic therapy and selection of antibiotics

Initiation of empirical antibiotic therapy while awaiting sepsis screen and blood culture result in at risk neonates is indicated. There is scant literature available regarding choice of antibiotics for EONS in developing countries. Ampicillin with gentamicin continues to be the recommended antibiotics [23,24]. If there is a concern for meningitis it is recommended to add cefotaxime to ampicillin. However, extensive use of cefotaxime has been associated with increased risk of invasive candidiasis [3]. It is acknowledged that ampicillin and gentamicin together may not be the most appropriate choice as there is an increasing prevalence of community extended spectrum beta-lactamase (ESBL) producers as the causative organisms of EONS [25]. Common pathogens like *Esherichia coli* and *Klebsiella* spp. show high degree of resistance to ampicillin [26]. A study on 187 neonates at risk for EONS comparing monotherapy with amikacin versus piperacillin-tazobactum in neonates at risk for EONS did not show any superiority of one antibiotic over the other. Therefore, empirical antibiotic therapy should be individualized for a hospital or region based on institutional antibiograms and epidemiological surveillance (Table 2) [27].

Duration of the therapy

Recommended duration of therapy using a penicillin or cephalosporin+aminoglycoside for blood culture positive EONS is 10-14 days. Treatment for meningitis due to gram negative bacteria is given for a minimum of 21 days or 14 days after a negative blood and CSF culture, whichever is longer. Focal infections such as osteomyelitis or endocarditis require even longer therapy [28]. The duration of antibiotic therapy in neonates with negative blood cultures is controversial especially in preterm neonates as they are considered to be at high risk for sepsis, and is not based on strong evidence. Antenatal and intrapartum antibiotic prophylaxis for suspected intra-amniotic infection may result in postnatal blood cultures being sterile i.e. false negative. In such cases the duration of therapy should be guided by the clinical course of the neonate and the risks associated with long course of antibiotics. Long duration of antibiotics in neonates with suspected sepsis and negative blood culture is associated with death and necrotizing enterocolitis [29]. The practice should be to withdraw antibiotics once blood cultures are found to be sterile by the end of 48-72 hours and there are no clinical or hematologic signs of infection. Studies have evaluated shorter courses of antibiotics in neonates with blood culture positive sepsis [30]. One pilot randomized study of probable sepsis in neonates >30 weeks gestation and >1000 gm weight compared short-course (48-96 hours) or long-course (7 days) antibiotic therapy. The study excluded infants with culture-positive sepsis and those who were symptomatic. There was no difference in treatment failure (defined as reappearance of signs of sepsis within 15 days of stopping antibiotics, supported by laboratory evidence) rate between the two groups [31-33].

	Actions
	Location: Delivery room
1	Ensure Antenatal steroid cover for all mothers at risk for preterm birth
2	Risk factor assessment of mothers for EONS
3	Avoidance of multiple vaginal examinations
4	Intrapartum antibiotic prophylaxis in mothers with identified risk factors
5	Short term tocolytics and Intravenous antibiotics in mothers with SPTOL*, pPROM**, PROM ≥ 18 hours to allow the course of antenatal steroids to be completed
6	Expectant management rather than Induced labour in mothers with pPROM at lower gestations. Each additional day increases neonatal survival by additional 2%
7	Clean delivery practices ensuring the '5 Cleans' and sterile resuscitation equipment for the newborn
8	Breast feeding initiation in the delivery room in at risk asymptomatic neonate ≥ 34 weeks
	Location: NICU
9	Sepsis screening of all at risk neonates
10	Sepsis screen with TLC, ANC, IT ratio, micro-ESR and CRP and repeating after 24 hours
11	Two negative serial CRP results (first between 8-24 hours age and second 24 hours later) strongly argue towards discontinuing antibiotic in the asymptomatic neonate
12	Clinical monitoring for neonates ≥ 34 weeks and antibiotic initiation if symptomatic
13	Empirical antibiotic therapy for neonates<34 week
14	Adding 1 ml blood to blood culture bottle
15	Starting an antibiotic based upon institutional antibiogram or local epidemiologic data
16	Treat culture positive sepsis for 14 days and exclude meningitis.
17	Total enteral feeding in babies >32 weeks who are asymptomatic
18	Avoidance of Intravenous fluids in preterms >32 weeks as a routine
18	Use of mothers own milk or donor milk and complete avoidance of formula milk
19	Strict hand washing and asepsis protocols for performing routine procedures like intravenous cannulation, OGT insertion and feeding etc.
*SPTOL: Spontaneous preterm onset of labour, pPROM: Preterm premature rupture of membranes, **PROM: Prolonged rupture of membranes	

Table 2: List of implementable actions to reduce the incidence of EONS.

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