Title:
Comparison of the Efficacy of a 7-day Versus 14-day Course of Intravenous Antibiotics in the Treatment of Uncomplicated Neonatal Bacterial Sepsis: a Randomized Controlled Noninferiority Trial

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METHODS

Study design

This is a multi-centric, randomized, active-controlled, non-inferiority trial. Stratification of subjects is done according to center and birth weight.

Eligibility

All neonates whose birth weight is more than 1000 grams with clinically suspected sepsis for which the treating physician decides to start antibiotics will be eligible for screening.

Inclusion Criteria

Subjects should satisfy all the following criteria:

- Neonates aged 0-28 days, either inborn or out born, who are currently admitted in the Neonatal unit of the centre,
- Whose birth weight is greater than 1000 grams (it should be reliably ascertained from records of a hospital.
- Whose residence is within approximately 15 kms from the centre, so that the infant can be brought back to the centre for follow up.
- Who have suspected septicemia for which a conventional or BACTEC/BACTALERT blood culture is sent and for which the treating physician decides to start antibiotics.

Exclusion Criteria

- Central Nervous System infection (meningitis will be defined as CSF Cells >25 per uL with polys >60%**OR [**(CSF glucose <20 mg/dL OR CSF:blood* glu ratio <0.6) **AND** (CSF protein >150 mg/dL in term OR >180 mg/dL in preterm)]
- Septic arthritis, osteomyelitis or deep-seated abscess as clinically judged by the treating team
- Life threatening congenital malformations as judged by the principal investigator of the centre

Parents of the subjects who satisfy the eligibility criteria are approached for participation in the study. They are provided a Patient Information Sheet for Enrolment (Appendix 1) and the nature and purpose of the observational part of the study will be discussed with them and they will be informed that they may be approached again for the randomized controlled trial portion of the study after approximately 7 days or more, if the infant meets criteria for randomization. The patient information sheet will also be discussed with the parents in a non-technical language. Written informed consent (3 copies) for enrolment will be taken from a parent in the presence of a witness (Appendix 2). One copy will be handed to the parent, one will be kept with the investigator and 1 will be kept in the hospital records. There will be no restrictions on the parent's right to ask questions related to the study. Patient-related data from start of screening up to eligibility for enrolment will be recorded in the "Screening sub-form" of Proforma A of case report form.

Data of observational part of the study

After obtaining consent for enrolment, the following data will be recorded: maternal and neonatal demographic data, maternal risk factors of sepsis, clinical and laboratory features of sepsis, culture and sepsis screen reports, antibiotics and their doses. The subjects will be followed up on a daily basis for remission of clinical signs (using a standard list of objectively defined signs), change of antibiotics (if any, with reasons), and co-interventions. Decisions regarding the kind of antibiotics and changes, if any, from the point of enrolment to the point of randomization will be left to the judgment of the treating physician.

Each of the participating Centres will decide on the empirical antibiotics based upon their standard empirical antibiotic policy. No changes in policy will be made for the sake of the research study. The antibiotics shall be stored, prescribed and dispensed as per the recommendations of Neofax essentials, 2014. All study subjects will receive routine care as per guidelines of the concerned centre.

Randomization criteria

Randomization will be done at the end of the 7th day of therapy with sensitive antibiotics. Of the enrolled subjects, only those who satisfy the criteria below will be randomized:

Eligible for randomization

- Positive blood culture other than *Staphylococcus aureus*
- No signs and symptoms of sepsis from end of day 5 through end of day 7 of starting sensitive antibiotics (This will be on day 5 through 7 for those who have improved and will be day 8 through 10 for those where in empiric antibiotics have been resistant requiring a change in antibiotic on day 3 of enrolment)

Not eligible for randomization

- Sterile blood culture
- Suspected contaminants in blood culture.
- Growth of *Staphylococcus aureus* in blood culture
- Growth of fungal organism in blood culture
- Diagnosis of meningitis, septic arthritis, osteomyelitis, abscess
- Has not gone into remission on day 5 or have recurrence of symptoms from day 5 through day 7
- If the empiric antibiotic is resistant but neonate has shown improvement of signs and symptoms of sepsis and there is ambiguity regarding in vivo sensitivity of antibiotic use

These elaborate criteria have been drawn up because this is an equivalence (non-inferiority) trial. In an equivalence trial, extra care has to be taken to exclude subjects who are likely to respond irrespective of which treatment arm they are in and also subjects who are not likely to respond irrespective of which treatment arm they are in. This is because inclusion of such patients would bias the results towards no effect (ie equivalence).

Data from enrolment until the point of determining eligibility for randomization will be recorded in the "Enrolment sub-form" of Proforma A of the case report form.

Randomization

Those eligible for randomization will be approached for consent for randomization. Parents will be provided Parent Information Sheet for Randomization (Appendix 3) and the details of the Randomized Controlled Trial will be discussed with them. Written informed consent (3 copies) for randomization will be taken from a parent in the presence of a witness (Appendix 4). One copy will be handed to the parent, one will be kept with the investigator and 1 will be kept in the hospital records. Subjects whose parents give consent for randomization will be randomly allocated to one of 2 groups:

Group A: Antibiotics will be stopped at the end of day 7.

Group B: The same antibiotics will be continued for a total of 14 days.

Those who do not satisfy the criteria for randomization and those whose parents do not give consent, will not be randomized and they will be followed up daily until clinical signs remit and will be administered the standard 14 days course of antibiotics.

Randomization procedure

Stratified, block randomization will be employed as described above. Randomly varying block sizes will be used and size of the blocks will be concealed until the end of the study. Each block will have equal number of allocations to Group A and Group B in a random sequence. Stratification will be by birth weight (1000-1499, 1500-2000g and >2000 g) and by Centre. Random number lists generated from a website http://randomizer.org will be converted into the sequence of allocation to the 2 Groups.

Concealment of allocation

Slips bearing the allocated Group will be placed in opaque envelopes, which will be sealed and numbered serially on the outside. There would be separate sets of such envelopes, one for each stratum (ie Center and birth weight group). In each center, envelopes will be opened in serial order, as each subject is included in the study. The name and identification details of the subject will be written on the outside of each envelope and all envelopes will be returned to the Principal Investigator in the nodal center.

Intervention

Among neonates who are allocated to group A, antibiotics will be stopped on day 7 of sensitive antibiotics (ie. immediately after randomization).

Among neonates who are randomized to group B, antibiotics will be continued until day 14 (ie for 7 more days after randomization).

If either of the groups develops signs and symptoms of sepsis, these babies will not be discharged, investigations will be done and appropriate antibiotics will be started. Each Centre will administer empirical antibiotics based upon their standard empirical antibiotic policy. No changes in policy will be made for the RCT. The antibiotics shall be stored, prescribed and dispensed as per the recommendations of Neofax essentials, 2014. All study subjects will receive routine care as per guidelines of the concerned centre.

Blinding

The following research team members will be blinded: the adjudicators of outcome and the laboratory personnel. The following will be unblinded: the principal investigator, the research staff, nurses and resident doctors involved in the care of the subjects in hospital. Data related to assessment of the outcomes will be recorded in a separate detachable part of the proforma (Proforma-part B). The pages of the proforma of a patient will have a unique identification number. Part B will be detached from the main proforma and handed to the adjudicators.

Follow-up

Any further hospitalization after stoppage of the antibiotic course would be at the discretion of the treating unit.

The follow-up period will extend from the point of randomization for 5 weeks (35 days). Details of all episodes of illness during this period (whether in hospital or after discharge) will be filled by the research staff. At the time of discharge, parents of all the babies will be given cards with the Investigators' names and contact information printed on them. Parents will be asked to report to the Newborn Unit for each episode of illness during the follow up period. Pediatric Emergency staff and Outpatient Department staff will also be informed about the special cards and asked to inform the Investigator in case such a baby reports for any illness.

In addition, all the babies will be followed up in the premises of the newborn unit at 48 hours (± 12 hours) for any signs of a sepsis syndrome. If the parents do not bring the baby for follow-up, the research staff will make a home visit. In addition, parents will be asked to bring the baby back to the Follow-Up Clinic by appointment on a weekly basis (± 2 days) for 35 days after randomization with particular emphasis on the visit at 28 days and 35 days. At each visit questions will be asked by the assessment team to ascertain whether an episode of a sepsis syndrome has occurred in the preceding week that required antibiotics. If the parents do not bring the baby back for weekly follow-up, the research staff will make a home visit.

Complete addresses & telephone numbers of the patients will be taken before discharge and babies who do not report in will be contacted at their homes.

All episodes of illness in a 35-day period after randomization will be evaluated for antibiotic treatment failure. A blood culture and sepsis screen (C reactive protein, complete blood counts,), procalcitonin, chest X-ray and CSF examination will be done, depending on the discretion of the treating physician. All clinical and laboratory details related to the episode of illness will be recorded on Proforma part B, detached and handed over to a blinded Neonatologist (adjudicator) to determine whether the episode qualifies to be a relapse of sepsis. In case any radiological imaging is performed, either digital (preferable) or hard copies of the images will be sent to the blinded Neonatologist at the nodal Centre after removing patient identifiers. In the event that the subject could not be brought back to the unit for the episode of illness, and treatment was received outside, every effort will be made by the assessment team to contact the treating physician and ascertain all details and such details will be entered in pro forma part B. Photocopies of lab reports and notes of other physicians will also be sent to the blinded neonatologist, after removing patient identifiers. Proforma part B will not contain any information by which the group of randomization may be ascertained.

Primary outcome variables

The primary outcome will be "definite relapse or probable relapse**".** Definite relapse will be defined as the occurrence of an episode of illness within the 21-day period after antibiotic completion in which the same organism with similar antibiogram is grown, as in the original episode. Probable relapse will be defined as the occurrence of an episode of illness within 21-day period that is diagnosed to be: Clinical diagnosis of bacterial sepsis, in the setting of a sterile blood culture. Part B of the proforma, along with all investigation reports will be mailed to the nodal center, where a Neonatologist who is unconcerned with the rest of the study, will be asked to adjudicate whether the concerned episode is a relapse or not.

Since this is a non-inferiority trial, the analysis will be done both as per protocol and as per intention to treat. Both the analyses will be reported, bearing in mind that the per protocol analysis is actually the more conservative of the two, with less bias towards "no effect".

In the per protocol analysis, the following subjects will be excluded from analysis:

a) In the 14-day group: patients whose 8^{th}- 14^{th} day of antibiotics could not be completed for any reason (including, but not limited to non-availability of cannula, a fresh episode of sepsis requiring change of antibiotics, withdrawal of consent or unscheduled discharge),
b) Subjects in either group whose primary outcome could not be assessed due to loss to follow-up or withdrawal of consent.

In the intention-to-treat analysis, all randomized subjects will be analyzed according to the group to which they were randomized, irrespective of compliance or change of antibiotics due to a fresh episode. Subjects in the 7-day group whose primary outcome could not be assessed due to loss to follow-up or

withdrawal of consent will be assumed to have definite relapse and those in the 14-day group to not have relapse.

Secondary outcomes

"Definite relapse" and "probable relapse" will be separate secondary outcomes, each assessed at 21 days and 28 days after antibiotic completion. [This was originally "definite or probable relapse"].

Episodes of relapses (# 1-4) will be analyzed both as per protocol and as per intention-to-treat:

1. "Definite relapse": by 21 days after antibiotic completion.
2. "Probable relapse": by 21 days after antibiotic completion.
3. "Definite relapse": by 28 days after antibiotic completion.
4. "Probable relapse": by 28 days after antibiotic completion.

Episodes of relapses (# 5-7) will be analyzed as per intention-to-treat:

5. "Definite or probable relapse" in the 28-day period after randomization and 35-day period after randomization
6. "Definite" in the 28-day period after randomization and 35-day period after randomization
7. "Probable" in the 28-day period after randomization and 35-day period after randomization]

The following will also be analysed in the 35-day period of observation after randomization:

(A) Episodes of secondary infections during the observation period. These may be bacterial or fungal.

(B) Adverse events: All fresh adverse events occurring after randomisation would be recorded. Adverse events with onset prior to randomisation would be recorded only if there is worsening after randomisation. Adverse events are listed and defined as per Appendix 5.

Sample Size Calculation

The sample size was calculated to be 350 in each arm based on the following assumptions: Event rate for the composite primary outcome of "definite or probable relapse" assumed to be 10% (combining both 7- and 14-day treatment arms) based on the earlier study (Chaudhary G, Dutta S, Narang A, Journal of Tropical Pediatrics 2006), non-inferiority margin of 7%, one sided alpha level as 5% and power of 90% and loss to follow- up of approximately 10%.

Mid-term analysis and stopping rules

The original was: Mid-term analyses will be performed after a total of one-third and two-third subjects are recruited. A separate Data Safety Monitoring Board will monitor serious adverse events in the trial and perform mid-term analyses at 1/3rd and 2/3rd recruitment. O'Brien-Fleming stopping rules and p values for superiority will be used for the interim analyses.

Data Safety Monitoring Board revised it to: DSMB will monitor serious adverse events in the trial and perform one interim analysis. The timing of this analysis would be based on either of the following: when about 50% of the expected primary outcomes have occurred (expected outcome events for the entire trial is 100 and therefore first interim analysis will be when approximately 50 events have occurred) or when 350 subjects have completed their follow-up as per protocol whichever is earlier. At the time of interim analysis, the DSMB will revisit the sample size of the study. O'Brien Fleming stopping criteria would be used for the primary outcome while Pocock's stopping rule for the serious adverse events.

If treatment failure rates are found significantly higher in the 7-day group in mid-term analysis, the trial will be stopped. If a death occurs due to bacteriologically confirmed relapse from the same organism

during the 28-day follow-up, the allocation group of that subject will be immediately ascertained. If it happens to be in the 7-day group, the trial will be stopped. The Data Safety Monitoring Board will also decide whether a death or other serious adverse event can be attributed to the intervention in the randomized controlled trial, and what compensation, if any, should be awarded.

Data analysis

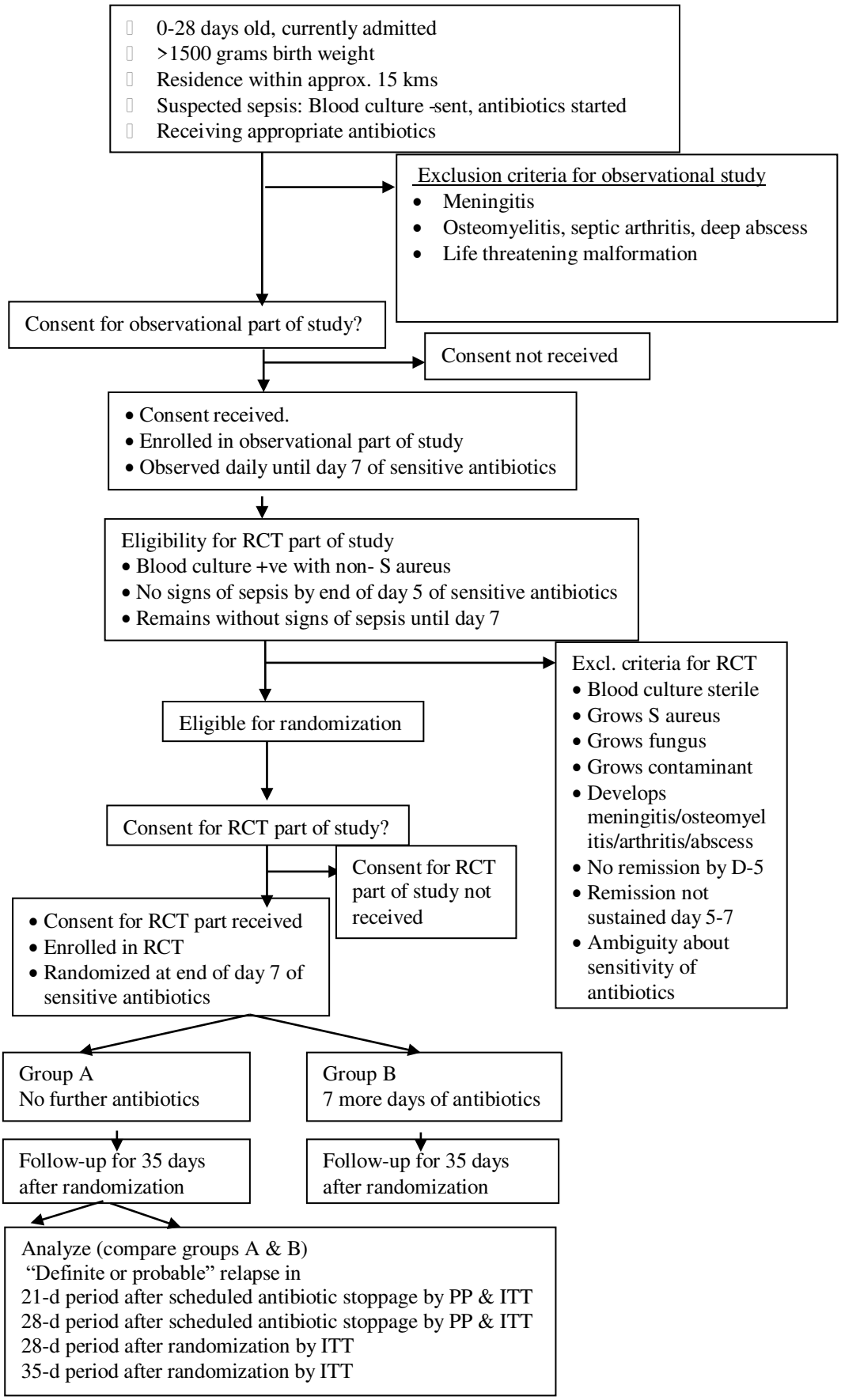
The baseline variables shall be described using descriptive statistics. As all the outcome variables are categorical, x^2 test with Yates correction or Fisher's Exact test as applicable will be used. Sub-group analysis has been planned for the following sub-groups: 1000-1500 g, 1501-2000 g, >2000 g, those infected with gram positive organisms and those with radiological pneumonia. For the sub-group analyses, level of significance will be kept as $p< 0.01$. Analysis shall be done using the statistical software packages SPSS version 10.

Quality control

Internal: All research officers and Principal investigators have undergone training in all aspects of the study 10% of Records are regularly checked by principal investigator or co-investigator in each centre10 % of computer data entry will be verified by Principal investigator and co-investigator

External: A Data safety monitoring board is constituted. Periodic meetings of the DSMB are held regularly.

TRIAL FLOW


0-28 days old, currently admitted
>1500 grams birth weight
Residence within approx. 15 kms
Suspected sepsis: Blood culture -sent, antibiotics started
Receiving appropriate antibiotics
Exclusion criteria for observational study
Meningitis
Osteomyelitis, septic arthritis, deep abscess
Life threatening malformation
Consent for observational part of study?
Consent not received
Consent received.
Enrolled in observational part of study
Observed daily until day 7 of sensitive antibiotics
Eligibility for RCT part of study
Blood culture +ve with non- S aureus
No signs of sepsis by end of day 5 of sensitive antibiotics
Remains without signs of sepsis until day 7
Excl. criteria for RCT
Blood culture sterile
Grows S aureus
Grows fungus
Grows contaminant
Develops meningitis/osteomyelitis/arthritis/abscess
No remission by D-5
Remission not sustained day 5-7
Ambiguity about sensitivity of antibiotics
Eligible for randomization
Consent for RCT part of study?
Consent for RCT part of study not received
Consent for RCT part received
Enrolled in RCT
Randomized at end of day 7 of sensitive antibiotics
Group A
No further antibiotics
Group B
7 more days of antibiotics
Follow-up for 35 days after randomization
Follow-up for 35 days after randomization
Analyze (compare groups A & B)
"Definite or probable" relapse in
21-d period after scheduled antibiotic stoppage by PP & ITT
28-d period after scheduled antibiotic stoppage by PP & ITT
28-d period after randomization by ITT
35-d period after randomization by ITT

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
1	Apnea		• Apnea needing methyl xanthine therapy or non-invasive respirator support	• Need of invasive respiratory support		• Death
	Definition: A disorder characterized by cessation of breathing for at least 20 seconds or accompanied by bradycardia					
2	AKI/ARF		• Serum creatinine increase of >=0.3 ma/dl within 48h OR • 1.5-1.9 times the lowest previous value within & days OR • Urine output(ml/kg/h):<0.5 for 12h	• Serum creatinine: 2-2.9 times the lowest previous value OR • Urine output (ml/kg/h):<0.5 for>=12 h	• Serum creatinine: >=3 times the lowest previous value OR • >=2.5 absolute value • Urine output (ml/kg/h): <0.3 for >=24 h OR anuria for >=12h • OR need of dialysis	• Death
	Definition: A disorder characterized by – Sudden impairment in kidney function that results in the inability to maintain adequate fluid, electrolyte, and waste product homeostasis					
3	Arrhythmias	• Incidental detection, transient and NOT causing cardiac shock and NOT needing any therapy	• Asymptomatic but need of medical therapy	• Symptomatic causing cardiac failure and need of medical therapy	• Symptomatic needing cardio version or surgical therapy	• Death
	Definition: A disorder characterized by abnormal heart rhythm diagnosed by ECG					
4	Anaemia	• Asymptomatic anaemia NOT needing blood transfusion		• Anaemia needing blood or exchange transfusion		

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
	Definition: A disorder characterized by abnormal heart rhythm diagnosed by ECG					
5	Accidental injury	• Minor external bleeding or injury,	• Need of minor surgery	• Fracture OR • Need of major surgery OR • Major bleeding • Significant intracranial bleeding	• Accomplished by cardiorespiratory compromise	• Death
	Definition: A disorder Characterized by injury to body due to accident like fall or violent contact with external object, including accidental asphyxia					
6	BPD	• Need of oxygen or respiratory support for at least 28 days but free of oxygen at 56 days/36 weeks PMA (mild BPD)	• Need of oxygen or respiratory support for at least 28 days but need of oxygen less than 30% at 56 days/36 weeks PMA (moderate BPD)	• Need of oxygen or respiratory support for at least 28 days but need of oxygen more than 30% or positive respiratory pressure at 56 days/36 weeks PMA (severe BPD)	• Severe BPD with frequent BPD spells, OR Persistent desaturations • Presence of cor pulmonale	• Death
	Definition: A disorder Characterized by prolonged (>28 days) requirement of oxygen therapy or respiratory support, respiratory distress and X-ray picture showing diffuse haziness or areas of hyperinflation and collapse/fibrosis					
7	Cholestasis/ hepatitis		• Asymptomatic cholestasis (TSB<12mg/dl)	• Cholestasis associated with complications like significant bleeding, encephalopathy, impairing growth OR • TSB 12mg/dL or more	• Cholestasis associated with hepatic failure	• Death

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
	Definition: A disorder characterized by inflammation of hepatic parenchyma and/or biliary tract which manifests as raised blood levels of liver enzymes and serum bilirubin					
8	Extravasation injury	• Skin erythema and small swelling of extremity	• Large swelling, OR • Superficial skin necrosis	• Deep skin necrosis		
	Definition: A disorder characterized by injury caused to skin due to extravasation of intravenous fluid					
9	Encephalopathy		• Transient (lasting less than 72 h) and mild abnormality in gestation – appropriate muscle tone, consciousness and reflexes, OR • HIE stage 1	• Prolonged (72h or more) OR • Moderate to severe, OR • HIE stage 2 abnormalities in gestation- appropriate muscle tone, consciousness and reflexes OR • Presence of seizures	• Encephalopathy causing cardiorespiratory compromise resulting in need of incubation or inotropic support, OR • HIE stage 3	• Death
	Definition: A disorder characterized by abnormality in muscle tone, consciousness and reflexes					
10	Gastroenteritis	• Gastroenteritis without dehydration	• Gastroenteritis with moderate dehydration	• Gastroenteritis with severe dehydration	• Gastroenteritis with shock	• Death
	Definition: A disorder characterized by inflammation of gastrointestinal tract manifesting as loose motions, vomiting, fever and dehydration. If gastroenteritis is a manifestation of sepsis- include it under heading of sepsis not under gastroenteritis heading.					

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
11	Gangrene		• Gangrene of distal phalanx	• Gangrene extending >1 phalanx of any digit or matacarpals/metatarsals	• Gangrene including long bones of limbs	
	Definition: A disorder characterized by gangrene of a part of body Note: if gangrene is caused due to sepsis, then sepsis may only be reported as SAE. However, if gangrene is caused due to sampling, in such cases, gangrene may be reported as SAE.					
12	Hypoglycemia	• Blood glucose 20-40 single episode, asymptomatic, treated with oral feeds	• More than one episode of blood glucose 20-40 mg/dL OR • Blood glucose<20 OR • Symptoms other than seizures OR • Need for glucose infusion up to 12 mg/kg/min	• Seizures OR • Need of intravenous glucose infusion @>12mg/kg/min or persisting for >7 days		
	Definition: A disorder characterized by blood glucose concentration less than 40 mg/dL					
13	Hyperglycemia	• NOT needing treatment with insulin	• Need of treatment with insulin	•		
	Definition: A disorder characterized by blood glucose concentration greater than 150mg/dL					
14	Hypothermia	• Axillary temperature 36.0°C-36.4°C	• Axillary temperature 32.0°C-35.9°C	• Axillary temperature <32.0°C		

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
	Definition: A disorder characterized by axillary temperature less than 36.5°C					
15	Hyperthermia	• Axillary temperature 37.6°C-38.0°C	• Axillary temperature 38.1°C-40.0°C	• Axillary temperature>40.0°C		
	Definition: A disorder characterized by axillary temperature more than 37.5°C					
16	Hypernatremia	• Serum sodium 146-150 mEq/L	• Serum sodium 151-160 mEq/L	• Serum sodium 161-170 mEq/L	• Serum sodium >170mEq/L OR • One accompanied by clinical features of seizures or altered consciousness	• Death
	Definition: A disorder characterized by increase in concentration of sodium ion in blood					
17	Hyperkalemia		• Serum potassium 5.5-6.5 mEq/L	• Serum potassium 6.5-8.0 mEa/L	• Serum potassium>8 mEq/L	• Death
	Definition: A disorder characterized by increase in concentration of sodium ion in blood					
18	Hyponatremia	• Serum sodium 130-134 mEq/L	• Serum sodium 120-129 mEq/L	• Serum sodium 110-119 mEq/L	• Serum sodium <110 mEq/L OR • One accompanied by clinical features of seizures or altered consciousness	• Death
	Definition: A disorder characterized by decrease in concentration of sodium ion in blood					

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
19	Hyperbilirubinemia	• Hyperbilirubinemia without need of therapy	• Hyperbilirubinemia needing treatment with phototherapy	• Hyperbilirubinemia needing treatment with blood exchange transfusion	• Hyperbilirubinemia with acute bilirubin encephalopathy	• Death
	Definition: A disorder characterized by increase in indirect bilirubin levels in blood					
20	Neutropenia (as per Manroe or Mouzihno chart)	• Asymptomatic NOT associated with systemic infection, NOT needing any therapeutic intervention	• Asymptomatic and NOT associated with systemic infection, but needing therapeutic intervention	• Associated with systemic infection		
	Definition: A disorder characterized by decrease (below gestation and postnatal age specific threshold) in number of neutrophils in peripheral blood film.					
21	NEC		• NEC stage 1 as per Walsh Kleigmann modification of Bell's classification	• NEC stage 2 per walsh Kleigmann modification of bell's classification	• NEC stage 3 as per Walsh Kleigmann modification of Bell's classification	• Death
	Definition: A disorder characterized by inflammation of gut which may progress to intestinal necrosis					
22	Osteopenia	• Asymptomatic NOT needing treatment	• Causing fracture or prolongation of respiratory support			
	Definition: A disorder characterized by formation of ulcers over pressure sites					

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
23	Pressure sore		• Small (<2cm)- healing happens in <1 week	• Major pressure sore (>2cm) and requiring surgical intervention or non-healing pressure sore		
	Definition: A disorder characterized by formation of ulcers over pressure sites					
24	Polycythemia	• Asymptomatic NOT needing treatment	• Symptomatic needing treatment with fluid relaxation or partial exchange transfusion	• Associated with complication such as NEC, thrombosis		
	Definition: A disorder characterized by increased haemoglobin or packed cell volume with haematocrit value 65% or more in blood as per gestation and postnatal gestation norms.					
25	Pleural effusion		• Minimal fluid in the pleural cavity requiring no/minimal change in respiratory support	• Free fluid in the pleural cavity requiring significant increase in respiratory support or requiring ICD drainage	• Fluid in pleural cavity resulting in circulatory collapse	• Death
	Definition: A disorder characterized by presence of free fluid in pleural cavity					
26	Peritonitis			• Peritonitis unaccompanied by perforation of gut	• Peritonitis accompanied by perforation of gut	• Death
	Definition: A disorder characterized by inflammation of peritoneal membranes.					

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
27	PDA	• Asymptomatic PDA	• PDA needing medical treatment	• PDA needing surgical treatment or resulting in cardiac failure	• PDA causing life threatening complications such as AKI, severe pulmonary haemorrhage NEC stage 3	• Death
	Definition: A disorder characterized by persistent non-closure of ductus arteriosus					
28	PVL	• Periventricular flare without cyst formation	• Periventricular leukomalacia with cysts formation in frontal, parietal regions	• Periventricular leucomalacia with cysts formation in occipital periventricular white matter		
	Definition: A disorder characterized by hypoxic-ischemic injury to periventricular brain resulting in disability					
29	Periventricular – intraventricular haemorrhage (P/IVH)	• Grade 1 IVH	• Grade 2 IVH	• Grade 3 IVH, OR • PVHI, OR • Any grade IVH manifesting as seizure or post haemorrhagic hydrocephalus	• Post – haemorrhagic hydrocephalus needing shunt placement, OR • IVH causing significant respiratory compromise requiring ventilation or hemodynamic compromise requiring vasopressors	• Death
	Definition: A disorder characterized by bleeding into periventricular – intraventricular space in brain					

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
30	Pulmonary hemorrage	• Occasional small bleed occurring spontaneously or during endotracheal suction requiring no/minimal change in respiratory support	• Recurrent small bleeds, does not require a transfusion/significant hike in respiratory support.	• Need for blood/component transfusion, OR • Need for significant augmentation of respiratory support, OR • Prolongation of ventilation	• Shock requiring vasopressors	• Death
	Definition: A disorder characterized by bleeding from the bronchial wall and / or lung parenchyma manifested as endotracheal bleeding or bleeding from mouth in a non- intubated baby.					
31	ROP	• Any ROP which is less severe than type ½ (this does not refer to stage 1 or 2) ROP.	• Type 2 ROP as described in ETROP study	• Type 1 ROP as described in ETROP study or ROP needing treatment		
	Definition: A disorder characterized by abnormal fibro vascular proliferation in retina Type 1 ROP – any of 3: (1) Zone I, any stage ROP with plus disease, (2) Zone I, stage 3 ROP without plus disease, or (3) Zone II, stage 2 or 3 ROP with plus disease Type 2 ROP – any of two : (1) Zone I, stage 1 or 2 ROP without plus disease, (2) Zone II, stage 3 ROP without plus disease					

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
32	Seizures		• Single episode of seizures without cardiorespiratory compromise due to transient metabolic abnormalities like hypoglycaemia, hypocalcaemia	• Multiple episodes of seizures OR • Seizures needing treatment with antiepileptic drug	• Status epilepticus OR • Seizures causing cardiorespiratory compromise	• Death
	Definition: A disorder characterized by abnormal involuntary movements of muscles					
33	Spontaneous Intestinal Perforation (SIP)			• SIP NOT needing surgical management by laparotomy and NOT • causing cardiorespiratory compromise	• SIP needing surgical management by laparotomy or leading • to cardiorespiratory compromise	• Death
	Definition: A disorder characterized by perforation of intestine without any clinical or intraoperative or pathological evidence of NEC					
34	Shock		• Hypotension or decreased organ perfusion lasting for <6 hours needing volume expander and resolving without consequence	• Hypotension or decreased organ perfusion needing /vasopressor(s)/ ionotropes	• Catecholamine resistant shock	• Death
	Definition: A disorder characterized by inability of circulatory system to meet metabolic requirement of tissues					

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
35	Sepsis (irrespective of etiology-bacterial, viral,fungal,protozoal) includes pneumonia, meningitis or bone-joint infection		• Culture negative sepsis, OR • Ventilator associated pneumonia requiring no/ minimal increase in respiratory support	• Culture positive sepsis OR • Meningitis OR • Encephalitis, OR • Presence of sclerema, OR • Ventilator associated pneumonia requiring • significant increase in respiratory support	• Septic shock requiring vasopressors, OR • Multi – organ dysfunction such as presence of AKI, DIC-bleeding, OR • Ventilator associated pneumonia resulting in • persistent desaturations despite high level ventilator support	• Death
	Definition: A disorder characterized by the presence of pathogenic microorganism in the blood stream that cause a rapidly progressing systemic reaction that may lead to shock and / or end organ failure					
36	Thromboembolism	• Asymptomatic , NOT needing treatment	• Causing gangrene of distal phalanx	• Causing gangrene extending > 1 phalanx of any digit or metacarpals/metatarsals	• Causing gangrene including long bones of limbs or any internal organ like brain, kidney or lungs	
	Definition: A disorder characterized by thromboembolic phenomenon involving a vascular system					
37	Thrombocytopenia	• NOT associated with bleeding and above the threshold for platelet transfusion	• NOT associated with active bleeding but needing platelet tranfusion	• Associated with bleeding or platelet count less than 20,000.	• Associated with intracranial bleeding	• Death

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
	Definition: A disorder characterized by decrease in number of platelets (less than 150,000/μL in peripheral blood					
38	Liver dysfunction	Asymptomatic raised liver liver enzymes, treatment not indicated	-	Symptomatic liver dysfunction	Decompensated liver function (e.g., ascites, coagulopathy, encephalopathy, coma)	Death
	Definition: A disorder characterized by a pathologic process involving liver parenchyma					
39	Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
	Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response.					

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
40	Hemolysis	Laboratory evidence of hemolysis only (e.g., direct antiglobulin test; DAT; Coombs'; schistocytes; decreased haptoglobin) ized by laboratory test results that indicate RBC destruction	Evidence of hemolysis and >=2 gm decrease in hemoglobin	Transfusion or medical intervention indicated (e.g., steroids)	Life-threatening consequences; urgent intervention indicated	Death
	Definition: Disorder characterized by widespread destruction of platelets					
41	Deranged coagulogram	INR or APTT >1 - 1.5 x ULN; INR >1 - 1.5 times above baseline if on anticoagulation	INR or APTT >1.5 - 2.5 x ULN; INR >1.5 - 2.5 times above baseline if on anticoagulation	INR or APTT >2.5 x ULN; INR >2.5 times above baseline if on anticoagulation	-	-
	Definition: A finding based on laboratory test results that indicate an increase in the ratio of the patient's prothrombin time to a control sample in the blood					
42	Disseminated intravascular coagulation	-	Lab findings of DIC with no bleeding	Laboratory findings and bleeding	Life-threatening consequences; urgent intervention indicated	Death
	Definition: a disorder characterised by systemic pathological activation of blood clotting mechanisms which result in clot formation throughout the body.					

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
43	Arthritis	Mild pain associated with erythema, inflammation	Moderate pain or joint swelling, limitation of movement	Severe pain associated with signs of inflammation, erythema or joint swelling; irreversible joint damage; disabling	-	-
	Definition: a disorder characterised by inflammation involving a joint					
44	Rash	Macules/ papules/ pustules covering <10% body surface area with or without symptoms	Macules/ papules/ pustules covering 10% - 30% body surface area with or without symptoms	Macules/ papules/ pustules covering >30% body surface area with or without symptoms	-	-
	Definition: a skin disorder characterised by the presence of macules or papules are pustules					
45	Superficial thrombophlebitis	-	Present	-	-	-
	Definition: a disorder characterised by a blood clot in inflammation involving a superficial vein of the extremities					
46	Urticaria	Urticarial lesions covering <10% BSA; topical intervention indicated	Urticarial lesions covering 10 30% BSA; oral intervention indicated	Urticarial lesions covering >30% BSA; IV intervention indicated		
	Definition: A disorder characterized by an itchy skin eruption characterized by wheals with pale interiors and well-defined red margins					

S. No	Adverse Event	Grades				
		1 (Mild)	2 (Moderate)	3 (Severe)	4 (Life Threatening)	5 (Death)
				(To be reported as SAE)		
47	Diarrhea	Increase of <4 stools per day over baseline	Increase of 4 - 6 stools per day over baseline	Increase of >=7 stools per day over baseline; incontinence; hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
	Definition: a disorder characterized by frequent watery bowel movements					
48	Vomiting	1 - 2 episodes (separated by 5 minutes) in 24 hrs	3 - 5 episodes (separated by 5 minutes) in 24 hrs	>=6 episodes (separated by 5 minutes) in 24 hrs; tube feeding, TPN or hospitalization indicated	Life-threatening consequences; urgent intervention indicated	Death
	Definition: A disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth					

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