Clinical Practice Guidelines

Use of Blood Components in Newborns

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Executive summary

Transfusion of blood products is a frequently performed intervention in the care of preterm and sick neonates in the neonatal intensive care unit (NICU). These may be packed red blood cells (PRBC) for treatment of anemia or platelet concentrates for thrombocytopenia or fresh frozen plasma (FFP) for management of a clinical coagulopathy. However, the rationale or the threshold for use of the blood components is not always well defined. A conservative approach and move towards adherence to restrictive thresholds is now being practiced by most neonatologists based on evidence from systematic reviews and meta-analysis. There are several concerns related to the use of blood products in neonates. Transfusion transmitted infections, acute circulatory overload, transfusion associated graft versus host disease (TA-GVHD) are some catastrophic complications which must make the neonatologist strongly consider the risk to benefit ratio prior to ordering a blood component transfusion. Provisioning of blood components requires presence of blood transfusion services or blood banks. Blood components are a precious, lifesaving and resource intensive therapy with limited availability. Hence there is all the more reason to be judicious and exact in its application. Recent high quality RCT on restrictive versus liberal thresholds for use of platelets, updated systematic reviews on erythropoiesis stimulating agents and delayed cord clamping provide good quality evidence for developing the guidelines on use of blood components. There is some difficulty in selecting the most appropriate measurement variable for determining the outcome in neonates e.g. using hemoglobin thresholds rather than tissue oxygenation for deciding for PRBC transfusion. Similarly, there are some difficulties in determining the normal parameters in different classes of neonates - preterm at varying degrees of prematurity and term neonates e.g. coagulation parameters.

The objective of this guideline is to provide an evidence based, objective document for use by neonatal clinicians and health care providers about the appropriate use of various blood components in order to reduce its unrestricted and irrational use and also highlight the various harmful effects of unrestricted and unscientific use. These guidelines have tried to address the most important questions pertaining to the use of blood components for which there may not be adequate clarity for the practicing neonatologists. These guidelines have also tried to address the values and considerations of blood component use by the various stakeholders such as neonatologists, nurses, parents and have also provided inputs about costs, resources, limitations and areas for further research. The guideline development group identified 14 foreground research questions of highest priority with 6 questions pertaining to use of PRBCs, 5 questions pertaining to FFP and cryoprecipitate transfusion and 3 questions related to transfusion of platelet components. There are 13 background questions which address interventions or effects of transfusion of the blood component e.g. delayed cord clamping and its effect on PRBC transfusion requirement or effect of platelet component transfusion. These questions are pertinent to preterm and term neonates as detailed in the guideline. The outcomes selected for each question were of clinical relevance and were considered to be either critical or important. The GRADE approach was used to examine the available evidence for risk of bias, inconsistency, indirectness and imprecision of the outcome of interest and then grade the quality (certainty) of evidence as high, moderate, low or very low. The guideline recommendations were made taking into account resource constraints, values and preferences of the stakeholders, feasibility and implementation considerations. Table 1 lists the key recommendations of the guideline.

Table 1: Summary of Recommendations for use of blood components in newborns

S.No.	Recommendations	Strength of recommendations	Quality of evidence
1.	Restrictive threshold packed red blood cell transfusion approach is strongly recommended in preterm neonates.	Strong	Moderate
2.	In neonates requiring packed red blood cell transfusion, smaller volume (10-15 ml/kg) is preferred.	Weak	Low
3.	Use of "fresh (< 7 days old) packed red blood cell only" for the transfusion is not recommended. The units should follow the existing standard practice used by the blood bank for issuing packed red blood cell (oldest first).	Strong	High
4.	Use of irradiated packed red blood cells and other cellular blood components is strongly recommended. It is more important to use irradiated products only in situations where the volume transfused is quite large (> 20 ml/kg).	Strong	Low
5.	The enteral feeds should be withheld in preterm neonates during packed red blood cell transfusion. The feed should be withheld three hours prior until the end of transfusion.	Weak	Moderate
6.	Provision of CMV safe blood for transfusion in preterm neonates by using CMV seronegative donors or leucoreduction or a combination of both is strongly recommended. For intrauterine transfusions use of CMV negative and leucodepleted packed red blood cell is strongly recommended.	Strong	Low
7.	A higher threshold (platelet count <25000/mm3) should be used for prophylactic platelet transfusions for prevention of major bleeding in preterm neonates.	Strong	Moderate
8.	In neonatal alloimmune thrombocytopenia (NAIT), maintaining platelet count >30,000/mm^3 is strongly recommended.	Strong	Very low
9.	The routine use of platelet transfusion for PDA closure in thrombocytopenic preterm neonates with hsPDA is not recommended.	Weak	Moderate

10.	The routine use of prophylactic fresh frozen plasma in preterm neonates is not recommended.	Strong	Low
11.	Prophylactic fresh frozen plasma transfusion (FFP) is not recommended in non-bleeding neonates receiving therapeutic hypothermia and having deranged coagulation parameters.	Strong	Moderate
12.	Neonates with deranged coagulation parameters and planned for surgical or invasive procedure should receive Fresh Frozen Plasma.	Strong	Very low
13.	Fresh Frozen Plasma(FFP) transfusion is preferred over Cryoprecipitate in the management of Disseminated Intravascular Coagulation. *Cryoprecipitate may be used if there is persistent hypofibrinogenemia (<1.0 g/L) despite FFP transfusion, rapidly falling fibrinogen, or major hemorrhage.*	Weak, Conditional	Low
14.	Routine coagulation profile screening for neonates admitted in the NICU is not recommended.	Strong	Very low

Introduction

Transfusion of blood products are required in nearly 50% of extremely low birth weight neonates and nearly 90% of all neonates admitted to the neonatal intensive care unit (1,2). Nearly 40% of preterm below 1500 gm and 95% below 1000 gm birth weight would receive a PRBC transfusion for correction of anemia (3) and this is one of the commonest therapeutic interventions in the NICU setting. Transfusion of platelet concentrates is the only specific readily available intervention for correction of thrombocytopenia. Fresh frozen plasma (FFP) transfusions have been employed for several indications such as management of disseminated intravascular coagulation (DIC), clinical bleeding with deranged coagulation parameters and also for management of hypovolemia.

The decision to transfuse a PRBC component can be made depending on the hemoglobin (Hb) or hematocrit (Hct) threshold or other markers like oxygen availability, fractional oxygen extraction or clinical features of anemia. The degree of respiratory support, frequency and severity of apnea, or rate of weight gain would also affect the decision to transfuse and the threshold for transfusion. Looking at Hb/ Hct for deciding on transfusion is practical and feasible and formed the basis for the trials comparing restrictive with liberal transfusion thresholds. For transfusing the preterm PRBCs should be washed, CMV negative, irradiated, leucodepleted, have a high Hct of >60%, preferably not greater than 7 days old since collection and issued in satellite bags from a single donor. Measures to prevent anemia in preterm neonates by providing placental transfusion at birth by delayed cord clamping (DCC), restricting blood sampling and micro-sampling is integral to the management of anemia.

Transfusion of platelet concentrates in neonates is guided by evidence of thrombocytopenia with or without clinical bleeding. The risk of bleeding in thrombocytopenic neonates is also affected by the etiology of the thrombocytopenia with a much greater risk for bleeding at higher platelet counts in immune-mediated thrombocytopenia. Prophylactic platelet transfusions in preterm neonates with thrombocytopenia at different thresholds require a change in our practices following the results of a recently published large well conducted RCT (4). Platelet concentrates may be derived from whole blood donations called random donor platelets (RDP) or isolated by apheresis called single donor platelet (SDP). Usually RDPs suffice in neonatal practice. Platelet concentrates require being stored at 22-24 degree Celsius with gentle agitation for up to 5 days. Platelet components are required to be irradiated prior to issue for use.

Transfusion of FFP in neonates has several indications even though the evidence supporting these practices is limited. Management of DIC, inherited deficiency of clotting factors, vitamin-K deficiency bleeding (prothrombin complex concentrates are preferable to FFP), prior to an invasive procedure in a neonate with coagulopathy, afibrinogenemia, deficiency of anti-coagulant proteins (congenital Anti-thrombin III deficiency, Protein-C and Protein-S deficiency) are approved indications. Use of FFP during therapeutic hypothermia for correction of coagulopathy without clinical bleeding, for volume replacement in hypotension, prevention of IVH in preterm or for performing a partial exchange transfusion for polycythemia is not recommended. After thawing the FFP has to be used immediately. However it may be stored at 4 degree Celsius for 24 hours after thawing. FFP is an abundant source of albumin, factor II, VII, X and XI while it contains insignificant amounts of antibodies, factor V, VIII and XIII.

Need for the guidelines

Differences in clinical care settings bringing about variations in clinical practice, perceived benefits of blood transfusion and availability of new evidence since the publication of the last clinical practice guideline in 2010 have necessitated the writing of this document. Studies on audit of transfusion practices have found a large proportion of transfusions for indications not supported by evidence-based guidelines (5,6) and a greater proportion of adverse events in infants compared to other age groups (7). The transfusion indications vary based on the gestational age, clinical context, and sickness level. Adapting guidelines developed by professional societies of other countries may have limitations in resource-limited countries like India (8).

Scope of the Guidelines and Target Audience

This document is intended to assist and guide health-care professionals in making clinical decisions about blood management in neonatal patients. Specific guidelines are needed for this age group because there are considerable physiological differences between neonates and children. These guidelines are intended to be used by neonatologists, pediatricians, general practitioners and staff nurses involved in newborn care. The document is written so that it can be applied to care-givers practicing at the wide range of newborn care facilities.

Questions relevant to clinical practice

The guideline development group (GDG) identified 14 research questions to be of the highest priority for development of recommendations through a poll amongst the members and a wider group of NNF members. The transfusion guidelines focus largely on aspects relating to common transfusion indications and administration of packed cells, platelets, fresh frozen plasma, and cryoprecipitate. The guidelines are applicable to preterm and term neonates admitted in the NICU. The guidance may not be appropriate for patients with certain rare disorders and does not cover unusual procedures, such as extracorporeal membrane oxygenation (ECMO). In all cases, individual patient circumstances may dictate an alternative approach.

A list of potential outcomes of interest for each question was circulated to all members of the GDG, who scored the importance of each outcome on a scale of 1 to 9 : 1–3: not important; 4–6: important; and 7–9: critical. The average of the scores for each outcome was used to prioritize the outcome and to select the most important outcomes for each PICO question.

The following questions have been addressed in this set of recommendations:

1. Should restrictive threshold for PRBC transfusion vs. liberal threshold for PRBC transfusion be used in preterm neonates?
2. Should small volume PRBC transfusion (10-15 ml/kg) vs. large volume PRBC transfusion (20 ml/kg) be used in neonates?
3. Should fresher PRBC transfusion vs. older PRBC transfusion be used in neonates?
4. Should irradiation of PRBC component vs. no irradiation of PRBC component be used for transfusion in neonates?
5. Should withholding enteral feeding vs. continued enteral feeding be used in preterm neonates receiving PRBC transfusion?

6. Should leucocyte reduction and CMV seronegative donor vs. no leucocyte reduction and CMV seronegative donor be used for transfusion of blood products in neonates?
7. Should low platelet count threshold < 25000/mm3 vs. high threshold < 50000/mm3 be used for prophylactic platelet transfusion in preterm neonates?
8. Should high platelet count threshold of > 30,000/mm3 vs. low threshold of < 30,000/mm3 be used for platelet transfusion in antibody mediated thrombocytopenia in neonates?
9. Should high platelet count threshold vs. low platelet count threshold be used in preterm neonates with patent ductus arteriosus?
10. Should fresh frozen plasma transfusion vs. no fresh frozen plasma transfusion be used for prophylaxis in preterm neonates?
11. Should fresh frozen plasma transfusion vs. no fresh frozen plasma transfusion be used in neonates with deranged coagulation receiving therapeutic hypothermia?
12. Should fresh frozen plasma transfusion vs. no fresh frozen plasma transfusion be used in neonates with deranged coagulation profile and surgery or invasive procedure?
13. Should cryoprecipitate vs. fresh frozen plasma be used in disseminated intravascular coagulation in neonates?
14. Should coagulation screening vs. no coagulation screening be used in neonates routinely?

Outcomes of interest

Question wise outcomes of interest are given in the detailed online annexure document . In summary, death in hospital or within 18 months, necrotizing enterocolitis, severe brain injury (IVH grade 4, PVL) , severe morbidity (IVH grade 3 or 4, BPD at 36 weeks, ROP needing treatment) and severe neurosensory adverse outcome were considered as *critical*. Post-transfusion increase in hemoglobin, hyperkalemia, apnea, number of transfusions and correction of laboratory abnormalities were considered as *important*.

Methodology

Group interaction and processes

The GDG brainstormed and developed a list of potential questions for the care domain in the PICO format (Patient, Intervention, Comparison, and Outcome) which were discussed threadbare and prioritized by survey amongst members of the wider group of NNF members. For each question, outcomes were identified and classified as critical or important. The group held multiple web meetings where editorial co-coordinators demonstrated the process of guideline building. The guidelines then went through a process of peer review and editorial review prior to publication.

Search strategy, data extraction and synthesis of evidence

Literature search was performed on PubMed, PubMed Central, Cochrane central trials registry and Google Scholar by using the relevant key words with Boolean operators of AND, OR and NOT. Studies were stratified according to type of intervention or exposure, study design, birth weight and gestational age where possible. Effects were expressed as relative risks (RR) or odds ratios (OR) for categorical data and as mean differences (MD) or weighted mean differences (WMD) for continuous data. Pooled effects estimates were calculated for developing the recommendations wherever feasible. All relevant reviews were summarized and the evidence

was synthesized using the GRADE methodology in the GRADE pro GDT Tool. Each study was analyzed for the outcome(s) and the identified studies were examined for the quality of the evidence (certainty) for the outcome using 6 parameters of risk of bias (limitations of study design and execution), inconsistency, indirectness, imprecision and others (publication bias, reporting bias, premature trial cessation etc.). The risk of bias was evaluated per study and across studies. Inconsistency was identified by the presence of heterogeneity between the studies, large variations in the effect, non-overlapping confidence intervals (CI) or a large (>60%) I^2. Indirectness was identified by differences between study populations in a systematic review, or difference in the way the intervention was given, differences in the outcome of interest or indirect comparisons. Small sample size, small number of events and wide CI identified imprecision. Based on these 6 parameters the Quality of evidence (certainty) was upgraded or downgraded and graded as: high, moderate, low or very low with the following interpretation:-

a. High: One can be sure that the intervention is beneficial, has no effect or is harmful. Results, including the magnitude of the pooled effect, are unlikely to change with new studies.
b. Moderate: One can be reasonably sure that the intervention is beneficial, has no effect or is harmful. However, the magnitude of the pooled effect may change with new studies.
c. Low: Although it is likely, one cannot be sure the intervention is beneficial, has no effect or is harmful. The magnitude of the pooled effect is uncertain and is likely to change with new studies.
d. Very low: One cannot be certain about the effects of the intervention.

Grading the quality of evidence

A two-step process was followed to draft the recommendations. In the first step the evidence was summarized in a tabular form (Summary of findings table) and quality of evidence assessed for all the questions. The writing group then considered the summary and quality of evidence for balance between benefits and harms, values and preferences for policy-makers, health care providers and parents, feasibility, resource use, cost-effectiveness and acceptability to formulate the recommendation for the question. Based on these considerations the writing group provided a judgment on the strength of each recommendation, categorized as strong or weak. Additionally, there are some conditional recommendations which are relevant when applied in a particular clinical circumstance or setting. A strong recommendation is one for which the panel is confident that the desirable effects of adherence to a recommendation outweigh the undesirable effects. This can be either in favor of or against an intervention. A weak recommendation is one for which the panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, but the panel is not confident about these trade-offs.

Questions, Evidence summaries and Recommendations

Practice Question 1 : Should restrictive threshold for PRBC transfusion vs. liberal threshold for PRBC transfusion be used in preterm neonates?

Summary of Evidence

The summary of findings table 2 given below includes 8 critical or very important outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from the Cochrane review on this question (10) which includes 4 RCTs (11, 12, 13, 14) and from 4 observational studies (15, 16, 17, 18) providing overall a moderate quality of evidence for the recommendation. PRBC transfusions given to neonates using hemoglobin thresholds based upon the nature of respiratory support (invasive ventilation or CPAP), degree of respiratory support (FiO2) and postnatal age using restrictive thresholds did not result in an increased risk of mortality, or composite outcome of death or severe morbidity and no increased risk of severe brain injury or severe neurosensory adverse outcome.

Table 2: Restrictive threshold for PRBC transfusion compared to liberal threshold for PRBC transfusion in preterm neonates

Patient or population: preterm neonates
Setting: NICU
Intervention: restrictive threshold for PRBC transfusion
Comparison: liberal threshold for PRBC transfusion

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with liberal threshold for PRBC transfusion	**Risk with restrictive threshold for PRBC transfusion**			
Death before discharge or within 18 months	142 per 1,000	**175 per 1,000** (122 to 251)	**RR 1.23** (0.86 to 1.76)	584 (3 RCTs)	⊕⊕◯◯ LOW [a,b,c,d]
Death or severe morbidity by first hospital discharge	671 per 1,000	**718 per 1,000** (644 to 805)	**RR 1.07** (0.96 to 1.20)	584 (3 RCTs)	⊕⊕⊕◯ MODERATE [d,e]
Death or severe brain injury by first hospital discharge	252 per 1,000	**282 per 1,000** (204 to 390)	**RR 1.12** (0.81 to 1.55)	614 (4 RCTs)	⊕⊕⊕◯ MODERATE [e]
Death by 18-21 months	175 per 1,000	**191 per 1,000** (133 to 274)	**RR 1.09** (0.76 to 1.56)	451 (1 RCT)	⊕⊕⊕⊕ HIGH
Severe neurosensory adverse outcome	220 per 1,000	**289 per 1,000** (198 to 418)	**RR 1.31** (0.90 to 1.90)	328 (1 RCT)	⊕⊕⊕⊕ HIGH
Incidence of apnea	664 per 1,000	**671 per 1,000** (631 to 718)	**RR 1.01** (0.95 to 1.08)	584 (3 RCTs)	⊕⊕⊕◯ MODERATE [a,e]

Table 2: Restrictive threshold for PRBC transfusion compared to liberal threshold for PRBC transfusion in preterm neonates

Patient or population: preterm neonates
Setting: NICU
Intervention: restrictive threshold for PRBC transfusion
Comparison: liberal threshold for PRBC transfusion

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with liberal threshold for PRBC transfusion	**Risk with restrictive threshold for PRBC transfusion**			
Postnatal weight change	The mean postnatal weight change was **0**	not pooled	-	511 (3 RCTs)	⨁⨁⨁◯ MODERATE [f]
Adaptive response to anemia	The mean adaptive response to anemia was **0**	not pooled	-	120 (4 observational studies)	⨁⨁◯◯ LOW [g,h,i]

The currently recommended Hb / Hct thresholds in preterm neonates for giving PRBC transfusion is as follows (New et al 2016):

Table 3: Hb (g/dl) / Hct (%) thresholds for PRBC transfusion in preterm neonates <32 weeks

Postnatal age	Ventilated	O_2 requirement / NIPPV	No respiratory support
First 24 Hours	12.0 (35)	12.0 (35)	10 (30)
Week 1	12.0 (35)	10 (30)	10 (30)
Week 2	10.0 (30)	9.5 (28)	7.5 (23) *
Week 3 and older	10.0 (30)	8.5 (25)	7.5 (23) *
*Clinical judgment may be used and transfusion may be given at a higher threshold of <8.5 g/dL.			

RECOMMENDATION 1

Restrictive threshold packed red blood cell transfusion approach is strongly recommended in preterm neonates. The panel recommends using above stated transfusion thresholds.

Strong recommendation, Moderate quality evidence

Practice Question 2 : Should small volume PRBC transfusion (10-15 ml/kg) vs. large volume PRBC transfusion (20 ml/kg) be used in neonates?

Summary of Evidence

The summary of findings table 3 given below includes 6 critical or very important outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from 3 RCTs (19, 20, 21) and 1 observational study (22) providing overall a low quality of evidence for the recommendation. Two critical outcomes had very low certainty, 2 had moderate certainty while the outcome with high certainty (post-transfusion increase in Hb) by itself does not translate into clinical relevance. Thus we rated the overall quality as Low. PRBC transfusion given to neonates at small volume did not result in an increased risk of death before discharge. There was no increased risk of ROP, PDA or BPD. There was only a modest increase in the post-transfusion hemoglobin following a large volume transfusion.

Table 4: Small volume PRBC transfusion (10-15 ml/kg) compared to large volume PRBC transfusion (20 ml/kg) in neonates

Patient or population: neonates
Setting: Neonatal Intensive Care Unit
Intervention: small volume PRBC transfusion (10-15 ml/kg)
Comparison: large volume PRBC transfusion (20 ml/kg)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with large volume PRBC transfusion (20 ml/kg)	**Risk with small volume PRBC transfusion (10-15 ml/kg)**			
Death before discharge	29 per 1,000	**26 per 1,000** (1 to 404)	**RR 0.89** (0.05 to 13.75)	72 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]
Retinopathy of prematurity	200 per 1,000	**200 per 1,000** (34 to 1,000)	**RR 1.00** (0.17 to 5.77)	20 (1 RCT)	⊕⊕⊕◯ MODERATE [d]
Bronchopulmonary dysplasia	429 per 1,000	**476 per 1,000** (176 to 1,000)	**RR 1.11** (0.41 to 2.96)	30 (1 RCT)	⊕⊕⊕◯ MODERATE [e]
Patent ductus arteriosus	100 per 1,000	**33 per 1,000** (2 to 732)	**RR 0.330** (0.015 to 7.320)	20 (1 RCT)	⊕◯◯◯ VERY LOW [b,d,f]
Post-transfusion increases in hemoglobin/ hematocrit	The mean increase was **0** g/dl	MD **1.4 g/dl lower** (2.49 lower to 0.31 lower)	-	22 (1 RCT)	⊕⊕⊕⊕ HIGH [g]
Hyperkalemia	The mean hyperkalemia was **4.7+-1.3** mmol/L	mean **0.2 mmol/L lower** (0.63 lower to 0.23 higher)	-	61 (1 observational study)	⊕⊕◯◯ LOW [h]

RECOMMENDATION 2

In neonates requiring packed red blood cell transfusion, smaller volume (10-15 ml/kg) is preferred.

Weak recommendation, Low quality evidence

Practice Question 3 :Should fresher PRBC (< 7 days old) transfusion vs. older PRBC (≥ 7 days) transfusion be used in neonates?

Summary of Evidence

The summary of findings table 4 given below includes 7 critical or very important outcomes and the effect size with 95% CI for the intervention and control. These have been obtained from the Cochrane review on this question (23) which includes 5 RCTs (24, 25, 26, 27, 28) providing overall a high quality of evidence for the recommendation. PRBC transfusions given to neonates using fresh RBCs did not result in a lower risk of death before discharge or composite disability of NEC, ROP, BPD or IVH. There was no decrease in risk of NEC-all stages or NEC-Stage 2 or greater. There was no reduction in risk of in-hospital infections both clinical and confirmed. Use of fresher RBCs reduced the donor exposure but did not reduce the number of transfusions per patient.

Table 5: Fresher PRBC transfusion compared to older PRBC transfusion in neonates

Patient or population: neonates
Setting: NICU
Intervention: fresher PRBC transfusion
Comparison: older PRBC transfusion

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with older PRBC transfusion	**Risk with fresher PRBC transfusion**			
Death before discharge	171 per 1,000	**187 per 1,000** (115 to 305)	**RR 1.09** (0.67 to 1.78)	490 (4 RCTs)	⊕⊕⊕◯ MODERATE [a]
Composite disability of NEC, ROP, BPD and IVH	529 per 1,000	**529 per 1,000** (434 to 640)	**RR 1.00** (0.82 to 1.21)	377 (1 RCT)	⊕⊕⊕⊕ HIGH
Necrotizing enterocolitis	88 per 1,000	**79 per 1,000** (41 to 152)	**RR 0.89** (0.46 to 1.72)	429 (2 RCTs)	⊕⊕⊕⊕ HIGH [b]
In-hospital Infection	656 per 1,000	**603 per 1,000** (531 to 689)	**RR 0.92** (0.81 to 1.05)	429 (2 RCTs)	⊕⊕⊕⊕ HIGH [c]

Donor exposure	The mean donor exposure was **4.4** donor exposures	MD **1.86 donor exposures fewer** (2.24 fewer to 1.48 fewer)	-	515 (5 RCTs)	⊕⊕⊕⊕ HIGH
Number of transfusions per patient	The mean number of transfusions per patient was **3.75** number of transfusions	MD **0.98 number of transfusions higher** (0.26 higher to 1.71 higher)	-	138 (4 RCTs)	⊕⊕⊕⊕ HIGH
Post-transfusion serum Potassium change	The mean post-transfusion serum Potassium change was **0.22** mmol/liter	MD **0.22 mmol/liter lower** (0.71 lower to 0.26 higher)	-	86 (3 RCTs)	⊕⊕⊕⊕ HIGH

RECOMMENDATION 3

Use of "fresh (< 7 days old) packed red blood cells only" for the transfusion is NOT recommended. Neonatal units should follow the existing standard practice of blood bank for issuing blood (oldest first approach).

Strong recommendation, High quality evidence

Practice Question 4 : Should irradiation of PRBC component vs. no irradiation of PRBC component be used for transfusion in neonates?

Summary of Evidence

The summary of findings table 5 given below includes 2 critical outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from 1 RCT (29) and 5 observational studies (30, 31, 32, 33, 34) providing overall a low quality of evidence for the recommendation. The exact incidence of Transfusion Associated-Graft versus Host Disease (TA-GVHD) in neonates following use of non-irradiated PRBCs is not known and is restricted to case reports only. TA-GVHD carries serious risk of mortality and morbidity. These case reports have in common an exposure of the neonate to large volume PRBC transfusions, which were not irradiated. Studies have shown a substantially higher level of potassium in the supernatant and extracellular fluid following storage of irradiated blood .

Table 6 : Irradiation of PRBC component compared to no irradiation of PRBC component for transfusion in neonates

Patient or population: transfusion in neonates
Setting: NICU
Intervention: irradiation of PRBC component
Comparison: no irradiation of PRBC component

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no irradiation of PRBC component	**Risk with irradiation of PRBC component**				
Transfusion associated GVHD	**Low**		not pooled	6 (5 observational)	⊕◯◯◯ VERY LOW [a]	
	not pooled	not pooled				
Hyperkalemia	The mean K was **5.9+-1.4** mmol/L	mean **10.6 mmol/L higher** (8.69 higher to 12.51 higher)	-	60 (1 RCT)	⊕⊕⊕◯ MODERATE [b]	

RECOMMENDATION 4

Irradiation of packed red blood cells and other cellular blood components for use in neonates is strongly recommended. It is even more important to use irradiated products in situations where the volume transfused is large (> 20 ml/kg). A strong recommendation is being made in the presence of low quality evidence because of the serious morbidity involved from using non-irradiated components.

Strong recommendation, Low quality evidence

Practice Question 5 :Should withholding enteral feeding vs. continued enteral feeding be used in preterm neonates receiving PRBC transfusion?

Summary of Evidence

The summary of findings table 7 given below includes 2 critical outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from a systematic review (35) which includes 7 observational studies (36, 37, 38, 39, 40, 41, 42) providing overall a moderate quality of evidence for the recommendation. Studies have shown that withholding of enteral feeding in preterm neonates undergoing a PRBC transfusion reduces the risk of TANEC stage 2 or more as compared to continued enteral feeding during the PRBC transfusion. DeRienzo et al (36) found that pretransfusion hematocrit was inversely related to risk of TANEC, suggesting a protective effect of maintaining higher baseline hemoglobin. Studies have shown a clinically relevant but statistically insignificant reduction in the incidence of NEC by withholding feeding during the PRBC transfusion. However, the entire evidence is obtained from observational studies and one small RCT.

Table 7: Withholding enteral feeding compared to continued enteral feeding for preterm neonates receiving PRBC transfusion?

Patient or population: preterm neonates receiving PRBC transfusion?
Setting: NICU
Intervention: withholding enteral feeding
Comparison: continued enteral feeding

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with continued enteral feeding	**Risk with withholding enteral feeding**			
Death before discharge	126 per 1,000	**95 per 1,000** (67 to 134)	**RR 0.75** (0.53 to 1.06)	1560 (2 observational)	⊕⊕⊕◯ MODERATE [a]
Transfusion associated NEC - Stage 2 or 3	24 per 1,000	**11 per 1,000** (7 to 19)	**RR 0.47** (0.28 to 0.80)	7492 (7 observational)	⊕⊕⊕◯ MODERATE [b]

RECOMMENDATION 5

Enteral feeds should be withheld in preterm neonates during packed red blood cell transfusion. The feeds should be withheld three hours prior to and until the end of transfusion.

Weak recommendation, Moderate quality evidence

Practice Question 6 : Should leucocyte reduction and CMV seronegative donor vs. no leucocyte reduction and CMV seronegative donor be used for transfusion of blood products in neonates?

Summary of Evidence

The summary of findings table 8 given below includes 2 critical outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from 4 observational studies (43, 44, 45, 46) providing overall a low quality of evidence for the recommendation**.** Studies have demonstrated that leukocyte reduction(LR) with use of CMV negative blood reduced the risk of transmission to 0%. A comparative study between LR and irradiation of blood product vs. not using LR and irradiated blood product showed a lower risk of Transfusion transmitted -CMV (2.5% vs. 10%) with LR and irradiation. These studies also show a reduction in the all-cause mortality. CMV infection in newborns carries serious short term and long term morbidity risks.

Table 8: Leucocyte reduction and CMV seronegative donor compared to no leucocyte reduction and CMV seronegative donor for transfusion of blood products in neonates

Patient or population: transfusion of blood products in neonates
Setting: NICU
Intervention: leucocyte reduction and CMV seronegative donor
Comparison: no leucocyte reduction and CMV seronegative donor

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no leucocyte reduction and CMV seronegative donor	**Risk with leucocyte reduction and CMV seronegative donor**			
Transfusion transmitted cytomegalovirus infection	not pooled	not pooled	not pooled	452 (4 observational)	⊕◯◯◯ VERY LOW [a,b]
Mortality (all causes)	not pooled	not pooled	not pooled	559 (2 observational)	⊕◯◯◯ VERY LOW [a,c]

RECOMMENDATION 6

Provision of CMV safe blood for transfusion in preterm neonates by using CMV seronegative donors or leucoreduction or a combination of both is strongly recommended.

For intrauterine transfusions use of CMV negative and leuco-depleted packed red blood cell is strongly recommended.

A strong recommendation is being made in the presence of low quality evidence because of the serious morbidity resulting from transfusion transmitted CMV infection in neonates.

Strong recommendation, Low quality evidence

Practice Question 7 : Should low platelet count threshold < 25000/mm3 vs. high threshold < 50000/mm³ be used for prophylactic platelet transfusion in preterm neonates?

Summary of Evidence

The summary of findings table 9 given below includes 5 critical or very important outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from 1 RCT (4) and 3 observational studies (47, 48, 49) providing overall a moderate quality of evidence for the recommendation. The PLANET-2 multi-centric trial by Curley et al (4) enrolling 660 neonates has shown the incidence of death and major bleed in the low threshold arm to be lesser as compared to the high threshold arm. This study did not report the incidence of IVH separately. There was a higher incidence of BPD in the high threshold group (63%) as compared to the low-threshold group (54%). Observational studies (47, 48, 49) have not shown a consistent relationship between platelet threshold and risk of IVH.

Table 9: Low platelet count threshold < 25000/mm3 compared to high threshold < 50000/mm3 for prophylactic platelet transfusion in preterm neonates

Patient or population: prophylactic platelet transfusion in preterm neonates
Setting: NICU
Intervention: low platelet count threshold < 25000/mm3
Comparison: high threshold < 50000/mm3

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with high threshold < 50000/mm3	**Risk with low platelet count threshold < 25000/mm3**			
Death up to 28 days	147 per 1,000	**105 per 1,000** (72 to 151)	**OR 0.68** (0.45 to 1.03)	656 (1 RCT)	⊕⊕⊕◯ MODERATE [a]

Table 9: Low platelet count threshold < 25000/mm3 compared to high threshold < 50000/mm3 for prophylactic platelet transfusion in preterm neonates

Patient or population: prophylactic platelet transfusion in preterm neonates
Setting: NICU
Intervention: low platelet count threshold < 25000/mm3
Comparison: high threshold < 50000/mm3

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with high threshold < 50000/mm3	**Risk with low platelet count threshold < 25000/mm3**			
Major bleeding up to 28 days of life	137 per 1,000	**103 per 1,000** (71 to 147)	**OR 0.72** (0.48 to 1.08)	658 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
Intraventricular hemorrhage – Gd. 3 or 4 (IVH)	not pooled	not pooled	not pooled	1363 (3 observational studies)	⊕◯◯◯ VERY LOW [b,c]
Bronchopulmonary dysplasia	628 per 1,000	**854 per 1,000** (813 to 886)	**OR 3.45** (2.57 to 4.62)	550 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
ROP stage 2 or more	276 per 1,000	**266 per 1,000** (215 to 323)	**OR 0.95** (0.72 to 1.25)	594 (1 RCT)	⊕⊕⊕◯ MODERATE [a]

The panel recommends following thresholds for platelet transfusion in preterm and term neonates (4, 56):

Platelet count (mm^3)	Indication for platelet transfusion
< 25000	Neonates with no bleeding (including neonates with Neonatal Allo-Immune Thrombocytopenia(NAIT) with no bleeding and no family history of ICH)
< 50000	Neonates with bleeding, current coagulopathy, before surgery, or infants with NAIT if previously affected sibling with intracranial hemorrhage
< 100000	Neonates with major bleeding or requiring major surgery (e.g. neurosurgery)

RECOMMENDATION 7

A higher threshold (platelet count <25000/mm^3) should be used for prophylactic platelet transfusions for prevention of major bleeding in preterm neonates.

Strong recommendation, Moderate quality evidence

Practice Question 8: Should high platelet count threshold of > 30,000/mm3 vs. low threshold of <30,000/mm3 be used for platelet transfusion in antibody mediated thrombocytopenia in neonates?

Summary of Evidence

The summary of findings table 10 given below includes 2 critical outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from 7 observational studies (50, 51, 52, 53, 54, 55, 56) providing overall a low quality of evidence for the recommendation. Observational studies have found the platelet count to be lower than 30,000/mm^3 in majority of the neonates who developed an intracranial hemorrhage.

Table 10 :High platelet count threshold of > 30,000/mm3 compared to low threshold of <30,000/mm3 for platelet transfusion in antibody mediated thrombocytopenia in neonates

Patient or population: platelet transfusion in antibody mediated thrombocytopenia in neonates
Setting:
Intervention: high platelet count threshold of > 30,000/mm3
Comparison: low threshold of <30,000/mm3

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with low threshold of <30,000/mm3	**Risk with high platelet count threshold of > 30,000/mm3**			
Intracranial hemorrhage	172 per 1,000	**828 per 1,000** (367 to 1,000)	**RR 4.80** (2.13 to 10.84)	58 (6 observational studies)	⊕◯◯◯ VERY LOW [a,b]
Mortality up to 28 days	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	(7 observational studies)	⊕◯◯◯ VERY LOW [b]

RECOMMENDATION 8

In neonatal alloimmune thrombocytopenia (NAIT), maintaining platelet count >30,000/mm^3 is strongly recommended.

A strong recommendation is being made in the presence of very low quality evidence because of the serious morbidity and long term neurodevelopmental sequelae arising from intracranial hemorrhage.

Neonates with NAIT requiring platelet transfusion should preferable receive single donor platelet (SDP) transfusions. Random donor platelets (RDP) may be however used in absence of SDP or in presence of bleeding while awaiting SDP.

Strong recommendation, Very low quality evidence

Practice Question 9 : Should high platelet count threshold vs. low platelet count threshold be used in preterm neonates with patent ductus arteriosus?

Summary of Evidence

The summary of findings table 11 given below includes 3 critical or very important outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from 1 RCT (57) providing overall a moderate quality of evidence for the recommendation. Observational studies had shown an association between low platelet counts and a significant PDA. However, recent well conducted RCT showed no difference between a liberal versus restrictive platelet transfusion in rate of closure of ductus in preterm neonates in first 5 days of life. There was also a much higher risk of developing some grade of IVH in the liberal transfusion group versus the restrictive group.

Table 11: High platelet count threshold compared to low platelet count threshold in preterm neonates with patent ductus arteriosus

Patient or population: preterm neonates with patent ductus arteriosus
Setting: NICU
Intervention: high platelet count threshold
Comparison: low platelet count threshold

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with low platelet count threshold	**Risk with high platelet count threshold**			
Closure of PDA	929 per 1,000	**864 per 1,000** (678 to 1,000)	**RR 0.93** (0.73 to 1.19)	29 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
Mortality (Death)	409 per 1,000	**360 per 1,000** (172 to 765)	**RR 0.88** (0.42 to 1.87)	44 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
IVH Grade3/4	91 per 1,000	**182 per 1,000** (36 to 892)	**RR 2.00** (0.40 to 9.81)	44 (1 RCT)	⊕⊕⊕◯ MODERATE [a]

RECOMMENDATION 9

The routine use of platelet transfusion for PDA closure in thrombocytopenic preterm neonates with PDA is not recommended.

Weak recommendation, Moderate quality evidence

Practice Question 10 : Should fresh frozen plasma transfusion vs. no fresh frozen plasma transfusion be used for prophylaxis in preterm neonates?

Summary of Evidence

The summary of findings table 12 given below includes 7 critical or important outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from 4 RCTs (58, 59, 60, 61) providing overall a low quality of evidence for the recommendation. Studies have not found a significant difference in mortality, severe disability, cerebral palsy or combined death or severe disability with FFP prophylaxis use in preterm neonates.

Table 12: Fresh frozen plasma transfusion compared to no fresh frozen plasma transfusion for prophylaxis in preterm neonates

Patient or population: prophylaxis in preterm neonates
Setting: NICU
Intervention: fresh frozen plasma transfusion
Comparison: no fresh frozen plasma transfusion

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no fresh frozen plasma transfusion	**Risk with fresh frozen plasma transfusion**			
Mortality till discharge	177 per 1,000	**196 per 1,000** (156 to 248)	**RR 1.11** (0.88 to 1.40)	692 (4 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]
IVH (any grade)/ICH till discharge	101 per 1,000	**64 per 1,000** (37 to 109)	**RR 0.64** (0.37 to 1.08)	654 (3 RCTs)	⊕◯◯◯ VERY LOW [a,b,c]
USG abnormalities assessed with: Ventriculomegaly or parenchymal echogenicity	132 per 1,000	**108 per 1,000** (67 to 174)	**RR 0.82** (0.51 to 1.32)	515 (1 RCT)	⊕⊕◯◯ LOW [a,c]
Death or Severe neurodevelopmental disability	295 per 1,000	**295 per 1,000** (247 to 365)	**RR 1.00** (0.84 to 1.24)	515 (1 RCT)	⊕⊕◯◯ LOW [a,c]
Proven sepsis	169 per 1,000	**287 per 1,000** (211 to 394)	**RR 1.70** (1.25 to 2.33)	428 (1 RCT)	⊕⊕⊕◯ MODERATE [a]
Patent ductus arteriosus	529 per 1,000	**593 per 1,000** (439 to 799)	**RR 1.12** (0.83 to 1.51)	38 (1 RCT)	⊕⊕◯◯ LOW [a,c]
Hypotension	149 per 1,000	**83 per 1,000** (48 to 144)	**RR 0.56** (0.32 to 0.97)	428 (1 RCT)	⊕⊕⊕◯ MODERATE [a]

RECOMMENDATION 10

The routine use of prophylactic fresh frozen plasma in preterm neonates is not recommended.

A strong recommendation is being made in the presence of low quality evidence because of the serious morbidities associated with transfusions, lack of any benefit and to dissuade the caregiver from this practice.

Strong recommendation, Low quality evidence

Practice Question 11 : Should fresh frozen plasma transfusion vs. no fresh frozen plasma transfusion be used in neonates with deranged coagulation receiving therapeutic hypothermia for perinatal asphyxia?

Summary of Evidence

The summary of findings table 13 given below includes 1 critical outcome and the effect size with 95% CI for the intervention and the control. These have been obtained from 15 observational studies (62-76) providing overall a moderate quality of evidence for the recommendation. Abnormalities of coagulation tests have limited predictive use for clinically significant bleeding. APTT, PT, INR and Fibrinogen levels may not accurately reflect the in-vivo condition of a patient undergoing therapeutic hypothermia.

Table 13: Fresh frozen plasma transfusion compared to no fresh frozen plasma transfusion in neonates with deranged coagulation receiving therapeutic hypothermia

Patient or population: neonates with deranged coagulation receiving therapeutic hypothermia
Setting: Perinatal asphyxia neonates undergoing therapeutic hypothermia in NICU
Intervention: fresh frozen plasma transfusion
Comparison: no fresh frozen plasma transfusion

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no fresh frozen plasma transfusion	**Risk with fresh frozen plasma transfusion**			
Major hemorrhage	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	1560 (15 observational studies)	⊕⊕⊕◯ MODERATE [a]

RECOMMENDATION 11

Prophylactic fresh frozen plasma transfusion (FFP) is not recommended in non-bleeding neonates receiving therapeutic hypothermia and having deranged coagulation parameters.

The decision to give FFP transfusion should not be based only on laboratory investigations; but also take into account the patient's clinical condition, potential risks (infection, volume overload, adverse effects) and benefits (bleeding prevention, continuing therapeutic hypothermia) of transfusion.

Strong recommendation, Moderate quality evidence

Practice Question 12 : Should fresh frozen plasma transfusion vs. no fresh frozen plasma transfusion be used in neonates with deranged coagulation profile and undergoing surgery or invasive procedure?

Summary of Evidence

The summary of findings table 14 given below includes 7 critical or important outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from 4 observational studies (5, 6, 77, 78) providing overall a very low quality of evidence for the recommendation. Studies have shown a correction of deranged PT, APTT and serum fibrinogen levels following FFP transfusion prior to surgery or invasive procedure in neonates with deranged coagulation profile. Surgical and invasive procedures carry a risk of bleeding.

Table 14 : Fresh frozen plasma transfusion compared to no fresh frozen plasma transfusion in neonates with deranged coagulation profile and undergoing surgery or invasive procedure

Patient or population: neonates with deranged coagulation profile and surgery or invasive procedure
Setting: NICU
Intervention: fresh frozen plasma transfusion
Comparison: no fresh frozen plasma transfusion

Outcomes	**Anticipated absolute effects*** (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no fresh frozen plasma transfusion	**Risk with fresh frozen plasma transfusion**			
Mortality	**Low**		not estimable	483 (3 observational studies)	⊕◯◯◯ VERY LOW
	0 per 1,000	**0 per 1,000** (0 to 0)			
IVH - any grade	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	298 (2 observational)	⊕◯◯◯ VERY LOW

Table 14 : Fresh frozen plasma transfusion compared to no fresh frozen plasma transfusion in neonates with deranged coagulation profile and undergoing surgery or invasive procedure

Patient or population: neonates with deranged coagulation profile and surgery or invasive procedure
Setting: NICU
Intervention: fresh frozen plasma transfusion
Comparison: no fresh frozen plasma transfusion

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no fresh frozen plasma transfusion	**Risk with fresh frozen plasma transfusion**			
Clinical bleeding	0 per 1,000	**0 per 1,000** (0 to 0)	not estimable	331 (2 observational)	⊕◯◯◯ VERY LOW
Correction of PT	The mean correction of PT was **0**	not pooled	-	32 (2 observational)	⊕◯◯◯ VERY LOW [a,b]
Correction of APTT	The mean correction of APTT was **0**	not pooled	-	34 (3 observational)	⊕◯◯◯ VERY LOW [c,d]
Correction of INR	The mean correction of INR was **0**	not pooled	-	33 (2 observational studies)	⊕◯◯◯ VERY LOW [e]
Change in fibrinogen levels	The mean change in fibrinogen levels was **0**	not pooled	-	26 (2 observational studies)	⊕◯◯◯ VERY LOW

RECOMMENDATION 12

Neonates with deranged coagulation parameters and planned for surgical or invasive procedure should receive Fresh Frozen Plasma.

Surgical and invasive procedures carry a substantial risk of major bleeding in presence of coagulopathy. Hence, a strong recommendation in spite of very low quality evidence.

Strong recommendation, Very low quality evidence

Practice Question 13 : Should cryoprecipitate vs. fresh frozen plasma be used in disseminated intravascular coagulation in neonates?

Summary of Evidence

The summary of findings table 15 given below includes 2 critical outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from 2 observational studies (79, 80) providing overall a low quality of evidence for the recommendation. Studies have shown greater resolution of DIC with cryoprecipitate when compared to FFP but this did not translate into better survival outcome. FFP transfusions may be associated with transfusion-associated circulatory overload.

Table 15: Cryoprecipitate compared to fresh frozen plasma in disseminated intravascular coagulation in neonates

Patient or population: disseminated intravascular coagulation in neonates
Setting: NICU
Intervention: cryoprecipitate
Comparison: fresh frozen plasma

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with fresh frozen plasma	Risk with cryoprecipitate			
Resolution of DIC assessed with: aPTT, PT and fibrinogen	636 per 1,000	**738 per 1,000** (458 to 1,000)	**RR 1.16** (0.72 to 1.86)	68 (2 observational studies)	⊕⊕◯◯ LOW [a,b,c]
Survival	545 per 1,000	**278 per 1,000** (142 to 556)	**RR 0.51** (0.26 to 1.02)	68 (2 observational studies)	⊕⊕◯◯ LOW [a,b,c]

RECOMMENDATION 13

Fresh Frozen Plasma(FFP) transfusion is preferred over Cryoprecipitate in the management of Disseminated Intravascular Coagulation.

Cryoprecipitate may be used if there is persistent hypofibrinogenemia (<1.0 g/L) despite FFP transfusion, rapidly falling fibrinogen, or major hemorrhage.

Weak Conditional recommendation, Low quality evidence

Practice Question 14 : Should coagulation screening vs. no coagulation screening be used in neonates routinely?

Summary of Evidence

The summary of findings table 16 given below includes 3 critical outcomes and the effect size with 95% CI for the intervention and the control. These have been obtained from 4 observational studies (5, 81, 82, 83) providing overall a very low quality of evidence for the recommendation. Observational studies have found the incidence of IVH and mortality to be similar between neonates undergoing routine screening vs. no screening.

Table 16 : Routine Coagulation screening compared to no routine coagulation screening in neonates

Patient or population: neonates routinely
Setting: NICU
Intervention: coagulation screening
Comparison: no coagulation screening

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no coagulation screening	**Risk with coagulation screening**			
Severe IVH (Grade3 and grade 4)	123 per 1,000	**178 per 1,000** (105 to 303)	**RR 1.44** (0.85 to 2.46)	310 (2 observational)	⊕◯◯◯ VERY LOW [a,b,c,d]
Mortality till discharge	219 per 1,000	**217 per 1,000** (142 to 329)	**RR 0.99** (0.65 to 1.50)	310 (2 observational)	⊕◯◯◯ VERY LOW [a,c]
No of FFP transfusions	373 per 1,000	**548 per 1,000** (489 to 612)	**RR 1.47** (1.31 to 1.64)	1167 (4 observational)	⊕◯◯◯ VERY LOW [a,b,c]

RECOMMENDATION 14

Routine coagulation profile screening for neonates admitted in the NICU is not recommended.

A strong recommendation is being given in view of no benefits, adverse effects and costs associated with unnecessary lab tests.

Strong recommendation, Very low quality evidence

Abbreviations

APTT: activated partial thromboplastin time	BPD: bronchopulmonary dysplasia	CPAP: continuous positive airway pressure
DCC: delayed cord clamping	DIC: disseminated intravascular clotting	ECC: early cord clamping
ECMO: extracorporeal membrane oxygenation	EPO: erythropoietin	ET: exchange transfusion
FFP: fresh frozen plasma	FNAIT: fetal-neonatal alloimmune thrombocytopenia	GRADE: Grading of Recommendations, Assessment, Development and Evaluation
HIE: hypoxic ischemic encephalopathy	ICH: intracerebral hemorrhage	INR: International normalized ratio
IUT: intrauterine transfusion	IVH: intraventricular hemorrhage	MAS; meconium aspiration syndrome
NEC: necrotizing enterocolitis	NICU: neonatal intensive care unit	NIRS: near infrared spectroscopy
PDA: patent ductus arteriosus	PRBC: packed red blood cells	PRP: platelet rich plasma
PT: prothrombin time	PVL: periventricular leukomalacia	RCT: randomized controlled trial
RDP: random donor platelets	ROP: retinopathy of prematurity	rSO2: regional saturation of oxygen
SDP: single donor platelets	TA-GVHD: transfusion associated- graft versus host disease	TACO: transfusion associated circulatory overload
TANEC: Transfusion associated necrotizing enterocolitis	TRALI: transfusion associated acute lung injury	TT-CMV: transfusion transmitted cytomegalovirus
UCM: umbilical cord milking		

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