Neonatal
पाठशाला

National Neonatology Forum
Gujarat State Chapter

Panel Discussion

16/02/2022, Wednesday | **03:30 pm - 04:30 pm**

Bleeding Neonate - An approach

Dr Sandip Trivedi
President, NNF Gujarat

Dr Prashant Kariya
Hon. Secretary, NNF Gujarat

Dr Ashish Mehta
Advisor

Dr Somashekhar Nimbalkar
Advisor

Dr Hiren Patel
Project Incharge

Dr Kedar Salweshwarkar
Moderator

Dr Naveen Bajaj
Expert

Dr Sachin Shah
Expert

Dr Chandrakumar
Expert

National Neonatology Forum

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BLEEDING NEONATE PANEL DISCUSSION

Moderator- Dr Kedar Sawleshwarkar

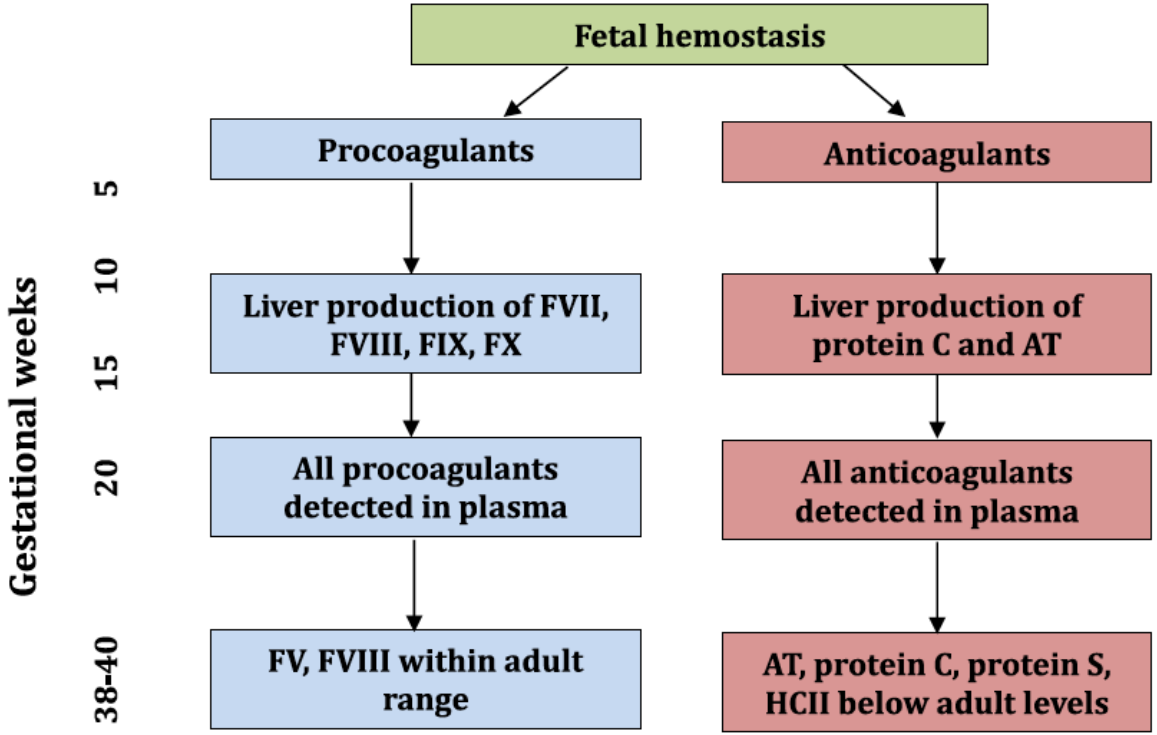
Panelist- Dr Naveen Bajaj,
Dr Sachin Shah,
Dr Chandrakumar

Developmental hemostasis

- The coagulation system is comprised of
  1)cellular elements (platelets being the most important)
  2)plasma proteins
- Work in concert to protect from both hemorrhage and thrombosis
- Concentration of plasma proteins are different in neonates when compared to older children and adults, and undergo rapid maturation over the first six months of life

- Procoagulant factors do not cross the placenta
- Fetus produces these factors in utero
- Measurable levels by 10 weeks' gestational age

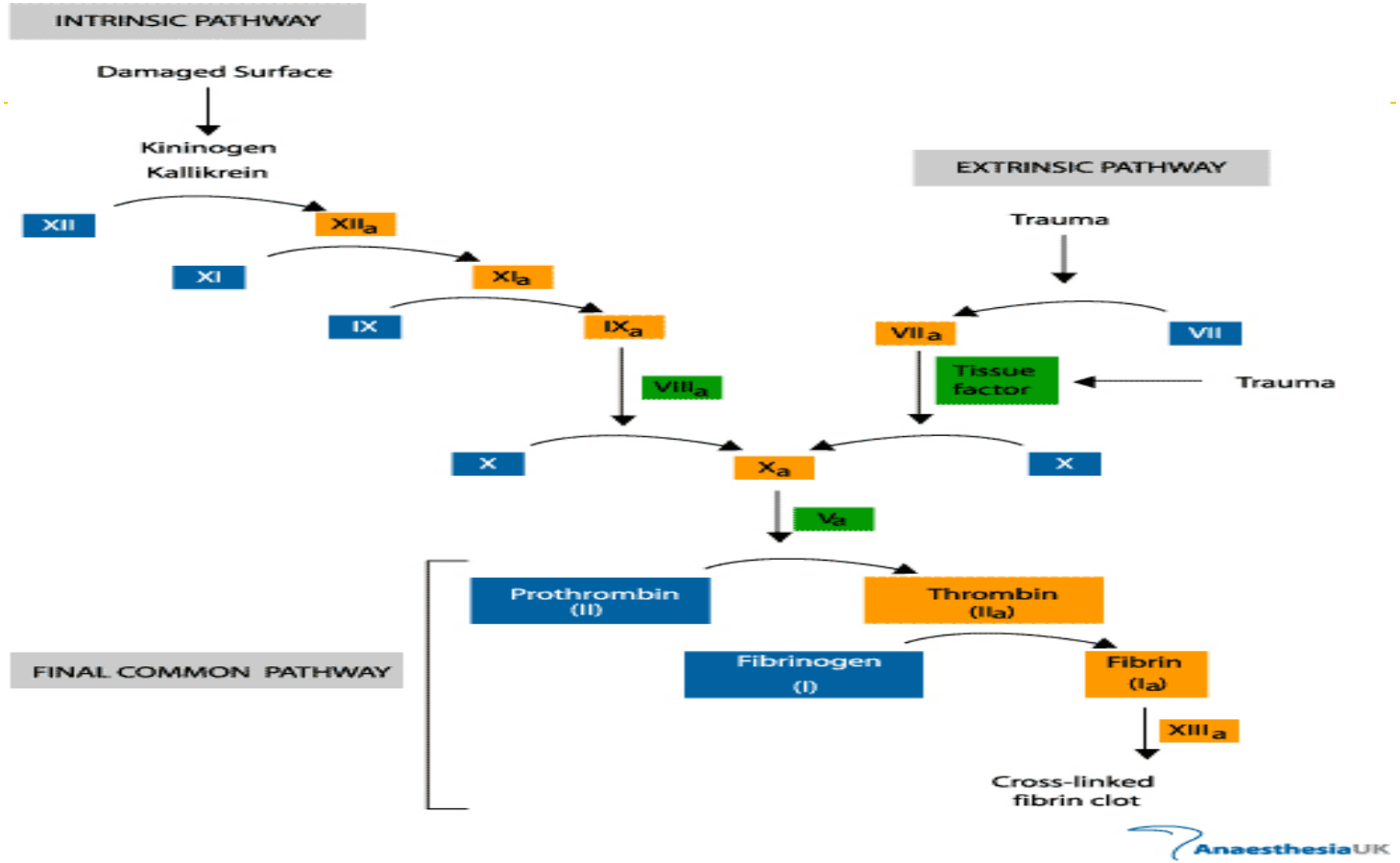
Fetal Hemostasis



Neonatal Coagulation / Anticoagulation / Fibrinolytic Protein Levels Compared With Adult Levels

	Protein Levels Elevated Compared With Adult Values	[d] Protein Levels Decreased Compared With Adult Values
Procoagulant	Fibrinogen Factor V[a] Factor VIII vWF	Factor II, VII, IX, X, XI, XII, XIII Prekallikrein High molecular weight kininogen
Anticoagulant	Alfa 2-micrglobulin	Antithrombin III Heparin Co-factor II Protein C Protein S
Fibrinolytic	Tissue plasminogen activator Plasminogen activator inhibitor	Plasminogen α2- antiplasmin

a-Factor V levels are Low on Day of life 1 but reach Adult values within days after birth (Will, 2015)
d-Levels are 50% of Adult values (Will, 2015)


INTRINSIC PATHWAY
Damaged Surface
Kininogen
Kallikrein
XII
XIIa
XI
XIa
IX
IXa
VIIIa
EXTRINSIC PATHWAY
Trauma
VIIa
VII
Tissue factor
Trauma
X
Xa
X
Va
FINAL COMMON PATHWAY
Prothrombin (II)
Thrombin (IIa)
Fibrinogen (I)
Fibrin (Ia)
XIIIa
Cross-linked fibrin clot
AnaesthesiaUK

Case 1- Dr Sachin Shah

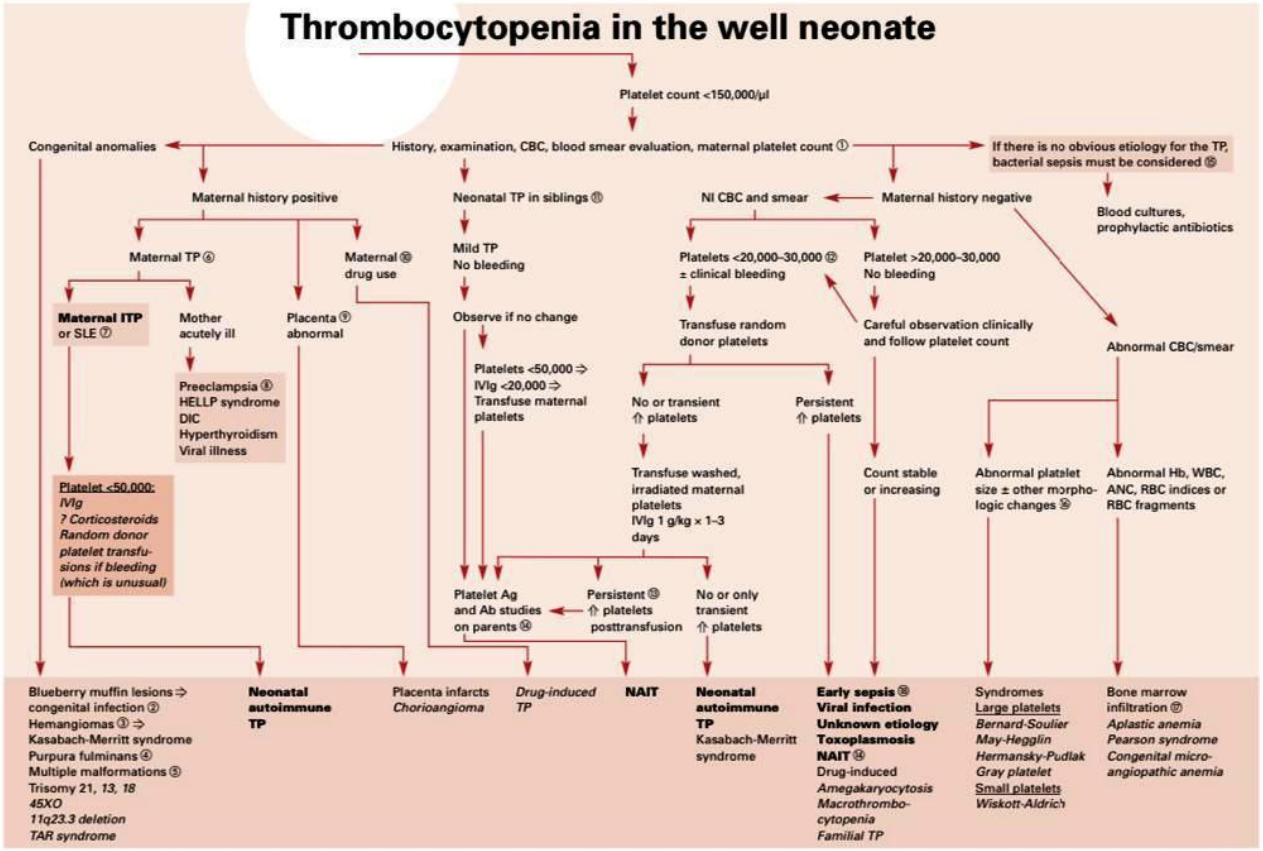
- Term AGA 3.5 kg, NVD, on breastfeeding
- D4- C/o lethargy, throws convulsions, Cranial USG – Gr 4 IVH
- Platelet count – 18000/cu mm Hb 10, TLC 12000, Sepsis screen negative

- Maternal platelet count 2,15,000/ cu mm
- No h/O bleeding disorder or ITP in the past

Spectrum of thrombocytopenia in healthy and sick neonates

Sick newborns	Well appearing newborns
Infection (bacterial, viral)	Alloimmune thrombocytopenia
Hypoxia	Maternal autoimmune disease
Respiratory distress syndrome	Infection
Pulmonary hypertension	Wiskott-Aldrich syndrome
Necrotizing enterocolitis	Amegakaryocytic thrombocytopen
Thrombosis	Trisomy 13, 18
Congenital heart disease	
Congenital leukemia	
Kasabach-Merritt syndrome	
TAR syndrome	

Thrombocytopenia in the well neonate

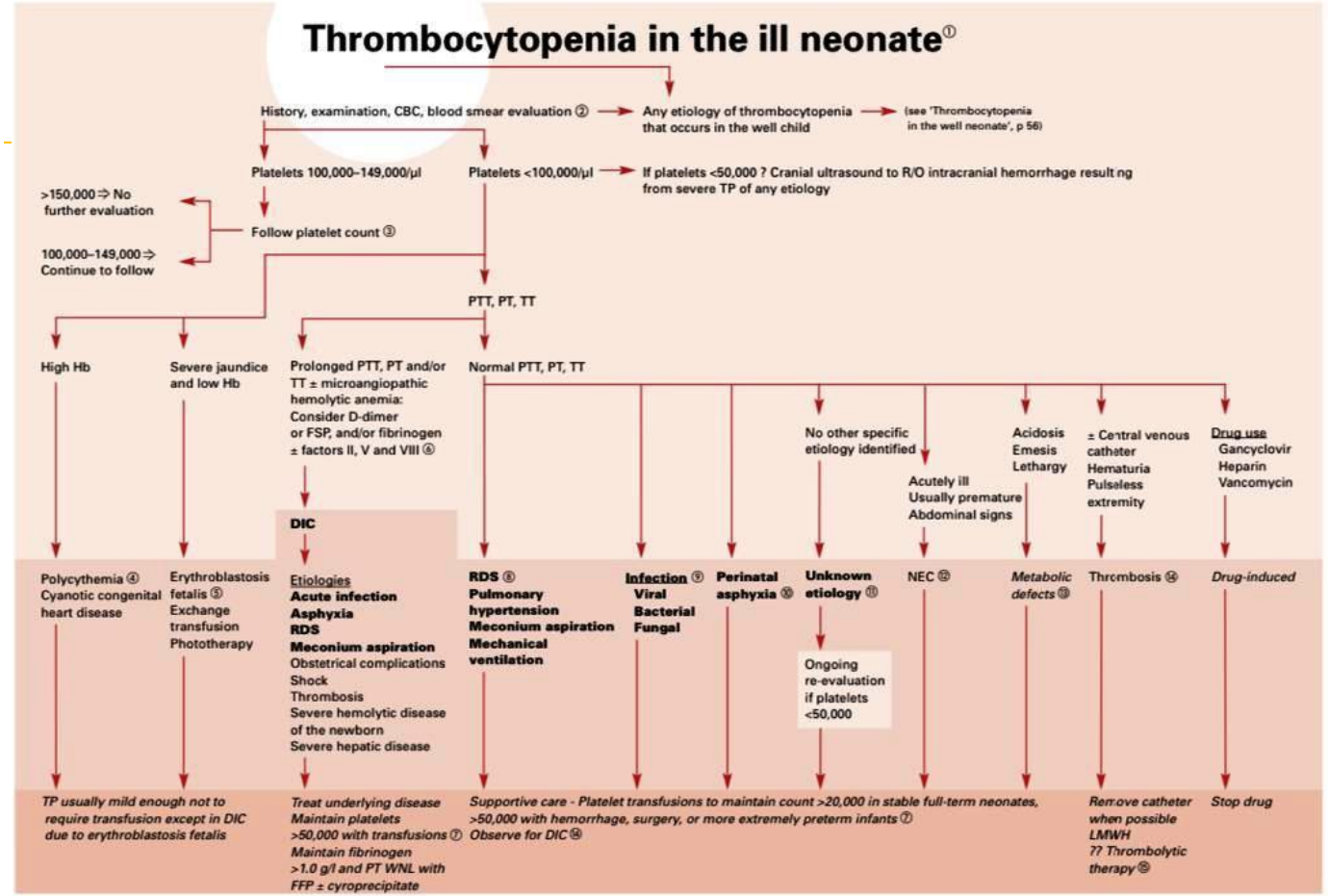


Case 2- Dr Chandrakumar

- ELBW SGA 31 week 850 gm, Primi with PET, Absent end-diastolic flow on umbilical flow. Platelet 1,10000.
- Vitals stable,
- Platelet count -Day 1- 94000, Day 2- 54000,

  Day-3 25000/cumm
- How will you proceed?
- Management?

Thrombocytopenia in the ill neonate①



CASE 3- Dr Naveen Bajaj

- Term AGA Male baby, 3 kg NVD, G2P1, No consanguinity
- ANC –uneventful, No h/o maternal medications
- CIAB, C/o vomiting of blood on day 2
- Baby active, Vitals normal

Sibling history

- H/o bleeding in sibling
- Term /Normal delivery
- Normal till 3 months
- Occasional bruises, healing by itself

On Examination

- Active, alert
- Vitals stable
- No pallor
- Icterus till abdomen
- No other bleeding manifestations

Investigations

- Hb-16.4
- TLC-15,500
- PLT-2,05,000

Differential diagnosis

Investigations

- PT-21.6
- INR- 1.8
- aPTT – 120 seconds

Diagnosis ???

- Further investigations
- Factor 8 < 1 %
- Factor 9 – 29.3
- Factor 13 – normal
- Sibling- K/c/o Hemophilia A, diagnosed at 11 months of age
- Factor 8 < 1%

Severe Hemophilia A

Case 4

- B/O XYZ
- Presented to us on day 12 of life
- H/o bleeding from umbilical stump from day 7

Maternal details

- 26 year old, primigravida
- Married since 1 year
- 3rd degree consanguineous marriage
- No h/o bleeding / recurrent blood transfusion in family
-

Obstetric history

- Regular ANC
- No h/o medical illness or fever with rash
- No h/o intake of any medications
- Antenatal scans – normal
- 20 wk scan – echogenic focus in heart
- Fetal Echo & Doppler - normal

Birth history

- 38.5 weeks, LBW, IUGR
- LSCS i/v/o Breech presentation at Local Hospital
- Boy, Birth weight – 2.2 kg
- Baby cried immediately after birth.
- APGAR – 1min-8, 5min-9
- Received Vit K at birth & shifted with mother

Postnatal history

- BF initiated within 30min, feeding well
- Jaundice, received phototherapy for 1 day
- D4 – discharged from hospital
- D7 – bleeding from umbilicus, intermittent, umbilical cord stump was intact, increases on manipulation
-

Dr Sachin Shah

- No other bleeding manifestations
- No h/o convulsions
- Approach?

At admission

- Baby clinically stable
- Feeding well
- No active bleeding

On Examination

- Vitals – stable
- GPE
- No cephalhematoma, subgaleal bleed
- No other bleeding manifestations
- Absent depressor Angularis oris
- Watery discharge from umbilicus +
- Systemic examinations –
  - PA – no organomegally
  - CVS/RS/CNS-WNL

INVESTIGATIONS

- CBC – Normal platelet count
- SEPSIS SCREEN – Negative
- LFT – Normal
- NSG – Normal

- Diagnosis – ? Dr Sachin Shah

Investigations

TEST	VALUE	REFERENCE RANGE - TERM
Platelets Count	3.05 Lakhs	1.5 – 4 Lakhs
PT	70.28	13 – 20 seconds
aPTT	63.4	30 – 45 seconds
INR	5.4	

Differential Diagnosis ??

- CLASSIC HEMORRHAGIC DISEASES OF NEWBORN

Presentation	Bleeding sites	Etiologies
Early (First 24 hr)	Scalp, subperiosteal, skin, intra-cranial, intrathorasic, intra-abdominal	Maternal drugs (e.g.- Warfarin, anticonvulsants)
Classical (Day 1-7)	Gastrointestinal, umbilical, skin, nose, circumcision	Mainly idiopathic, Breastfeeding (Low milk intake)
Late (Day ≥8, peak 3-8 weeks)	Intracranial, skin, Gastrointestinal	Idiopathic or secondary, exclusive breast feeding in the absence of Vit K administration, undiagnosed cholestasis often present. Secondary cases from malabsorption resulting from underlying disease (e.g. – Biliary atresia, α-1-antitripsin, cystic fibrosis) or chronic diarhea, Antibiotic therapy sometimes indicated

Laboratory abnormalities

PT	↑ ↑
INR	↑
PLATELETS	Normal
FIBRINOGEN	Normal
D-DIMER	Normal
APTT	↑ Severe form

- Improvement of PT and aPTT within 24 hrs after administering parental Vit K – confirmatory

TESTS	DAY 8	DAY 9
PT	70.28 seconds	12 second
aPTT	63.4 seconds	35 seconds
INR	5.4	1.1
TREATMENT	Vit K FFP CRYO	

TESTS	DAY 8	DAY 9	Day 11
PT	70.28 seconds	12 second	80 seconds
aPTT	63.4 seconds	35 seconds	68.6 seconds
INR	5.4	1.1	6.2
TREATMENT	Vit K FFP CRYO		

Dr Naveen Bajaj

- Approach?

FACTOR ASSAYS	
Factor 8 activity	60 %
Factor 9	49.3 %
Factor 13	Absent

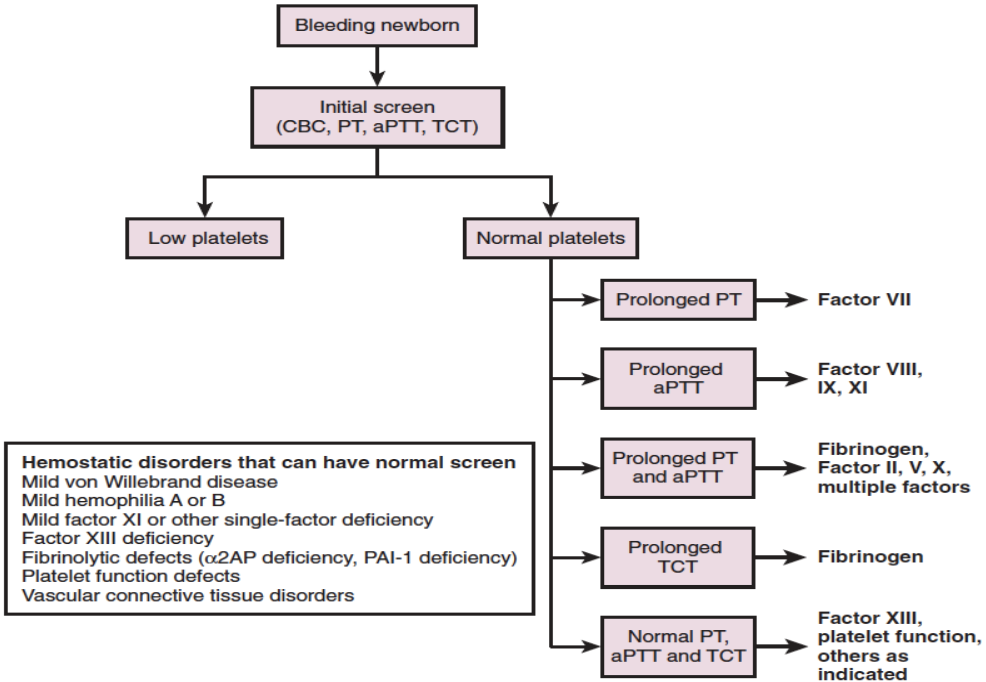
- Factor 13 deficiency – umbilical stump bleeding in 50 -70 % cases
- Low Factor 13 do not prolong PT and aPTT

TESTS	VALUE DAY 8	DAY 9	DAY 11	DAY 15
PT	70.28 Seconds	12 Seconds	80 Seconds	180 Seconds
aPTT	63.4 Seconds	35 Seconds	68.6 Seconds	120 Seconds
INR	5.4	1.1	6.2	12
TREATMENT GIVEN	VIT K FFP CRYO			

- Planned complete coagulation work up
- Bleeding from prick sites
- Cryo precipitate transfused
- Coagulation profile was repeated

TESTS	VALUE DAY 8	DAY 9	DAY 15	DAY 20
PT	70.28 Seconds	12 Seconds	180 Seconds	12.9 Seconds
aPTT	63.4 Seconds	35 Seconds	120 Seconds	33.1 Seconds
INR	5.4	1.1	12	1.08
TREATMENT GIVEN	VIT K FFP CRYO			

Dr Chandrakumar



• **Fig. 79.12** Approach to laboratory evaluation of coagulation in neonates. aPTT, Activated partial thromboplastin time; CBC, complete blood count; PT, prothrombin time; TCT, thrombin clotting time.

- THROMBIN TIME – 40 SEC N- < 21 SEC

Provisional Diagnosis

- CONGENITAL FIBRINOGEN DISORDERS
- Plan → complete coagulation profile after 3 weeks

Rapid fire

- 27 week, RDS on ventilator, Pulmonary hemorrhage?
- 29 week SGA 780 gm, stable till day 7, develops prolonged bleeding from venepuncture site.
- Indications for FFP in newborn- Dr Sachin Shah
- Indications for Cryoprecipitate- Dr Chandrakumar
- Threshold for platelet transfusion- Dr Naveen Bajaj

APPROACH TO A BLEEDING NEONATE

1. Detailed history including detailed past history and family history.
2. A careful physical examination.
3. Screening tests.
4. Specific tests for hemostasis as required

HISTORY

- Consanguinity
- Family H/O bleeding disorders

INHERITED	ACQUIRED
HEMOPHILIA	Vitamin K Deficiency
VON WILLEBRAND DISEASE	Disseminated Intravascular Coagulation
FACTOR 2, 5, 7, 10,11,13 DEFICIENCY	Coagulopathy of Acute Liver Disease
AFIBRINOGENEMIA	

INHERITED ABNORMALITY OF CLOTTING FACTORS		
X - LINKED	AD	AR
Hemophilia A	Von Willebrand disease	Deficiency of F11,7,5,10,2,fibrinogen and F 13
Hemophilia B	Dysfibrinogenemia	

- H/o maternal medications-
- Anticonvulsants(phenytoin, phenobarbitone), Salicylates, warfarin → interfere with the effect of Vit K on clotting factors
- History of prior pregnancies and their outcomes
- Maternal H/o thrombocytopenia

ON EXAMINATION

Well infant	Sick infant
VKDB	DIC
Clotting factor deficiency.	Infection
Immune thrombocytopenia	Liver diseases
Platelet functional disorders	NEC
Vascular causes	

- Petechiae, small ecchymosis – platelet disorder
- Large bruises – clotting factors defeciency, DIC, liver disorders or vit k deficiency
- Spleenomegaly – congenital Infection/erythroblastosis.
- Jaundice/cholestasis –TORCH infections or LIVER disease
- Abnormal retinal finding-TORCH infection

INVESTIGATIONS

- FIRST LINE

1. Complete blood count,
2. aPTT
3. Prothrombin time (PT)
4. Thrombin time, and
5. Fibrinogen level

- SECOND LINE

1. Factor XIII
2. Mixing studies

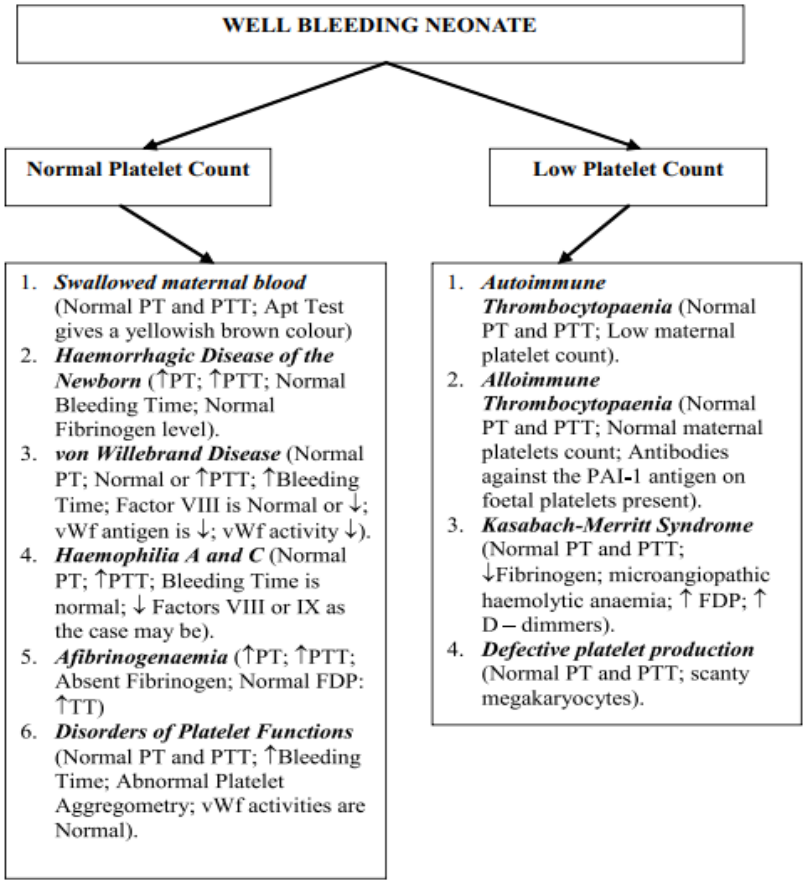
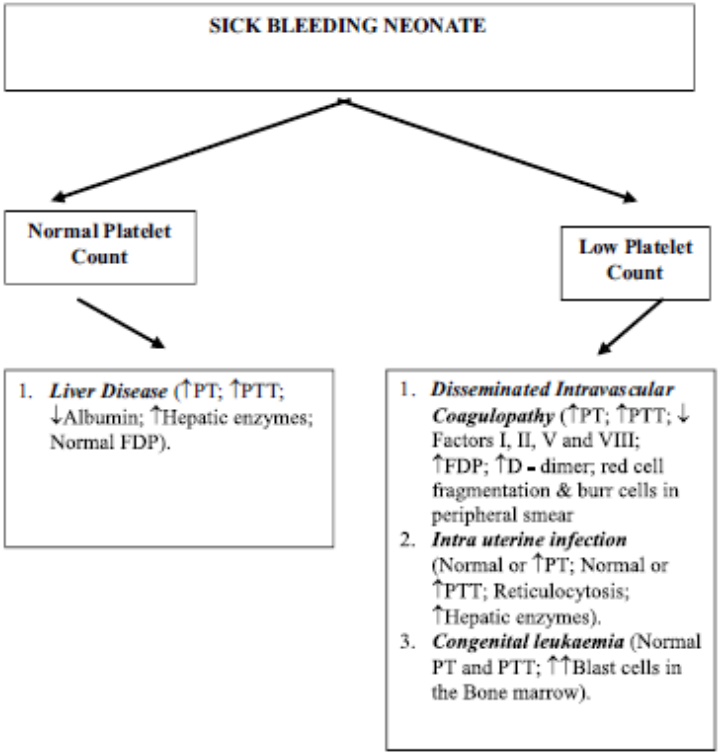
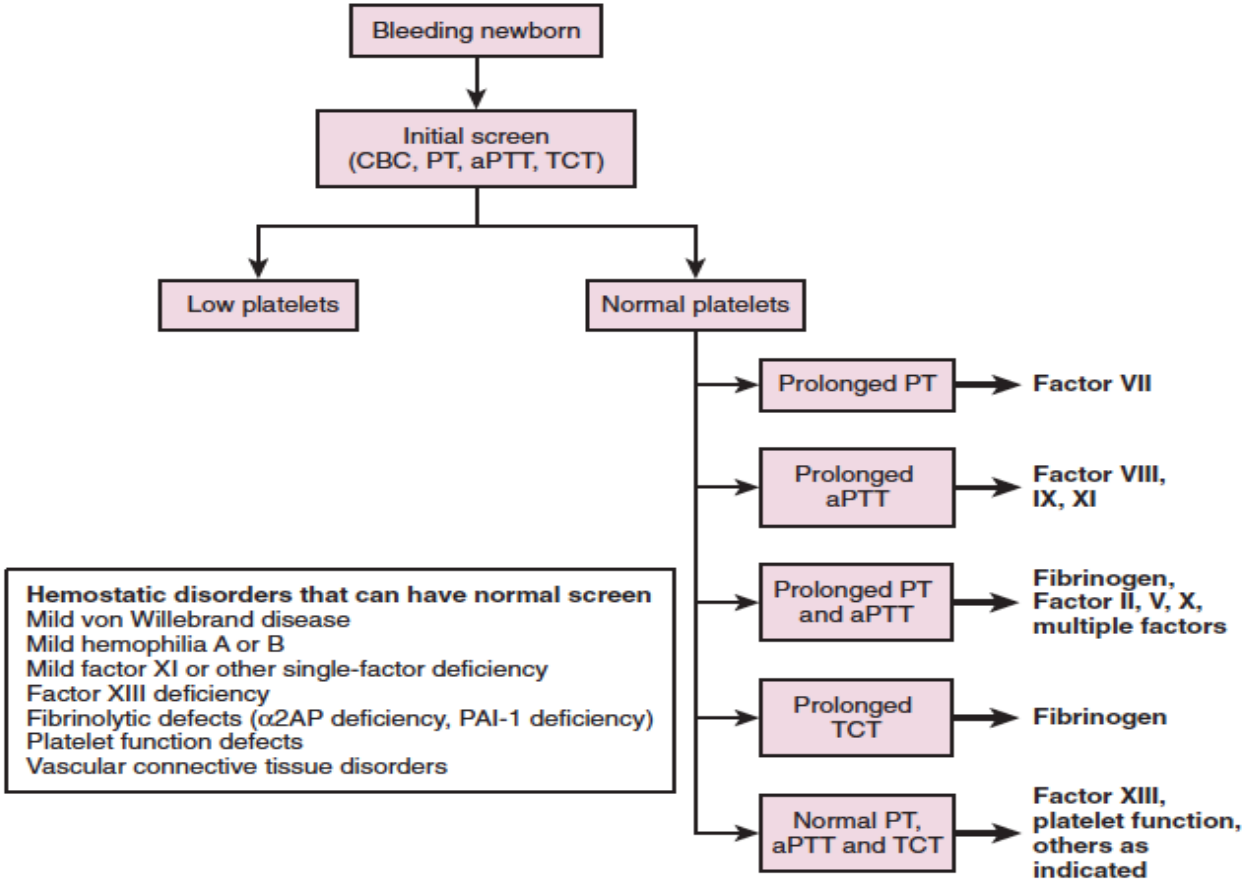


Figure 1: Evaluation of a well bleeding neonate


SICK BLEEDING NEONATE
Normal Platelet Count
Low Platelet Count
1. Liver Disease (↑PT; ↑PTT; ↓Albumin; ↑Hepatic enzymes; Normal FDP).
1. Disseminated Intravascular Coagulopathy (↑PT; ↑PTT; ↓ Factors I, II, V and VIII; ↑FDP; ↑D – dimer; red cell fragmentation & burr cells in peripheral smear
2. Intra uterine infection (Normal or ↑PT; Normal or ↑PTT; Reticulocytosis; ↑Hepatic enzymes).
3. Congenital leukaemia (Normal PT and PTT; ↑↑Blast cells in the Bone marrow).


Bleeding newborn
Initial screen (CBC, PT, aPTT, TCT)
Low platelets
Normal platelets
Prolonged PT
Factor VII
Prolonged aPTT
Factor VIII, IX, XI
Prolonged PT and aPTT
Fibrinogen, Factor II, V, X, multiple factors
Prolonged TCT
Fibrinogen
Normal PT, aPTT and TCT
Factor XIII, platelet function, others as indicated
Hemostatic disorders that can have normal screen
Mild von Willebrand disease
Mild hemophilia A or B
Mild factor XI or other single-factor deficiency
Factor XIII deficiency
Fibrinolytic defects (α2AP deficiency, PAI-1 deficiency)
Platelet function defects
Vascular connective tissue disorders

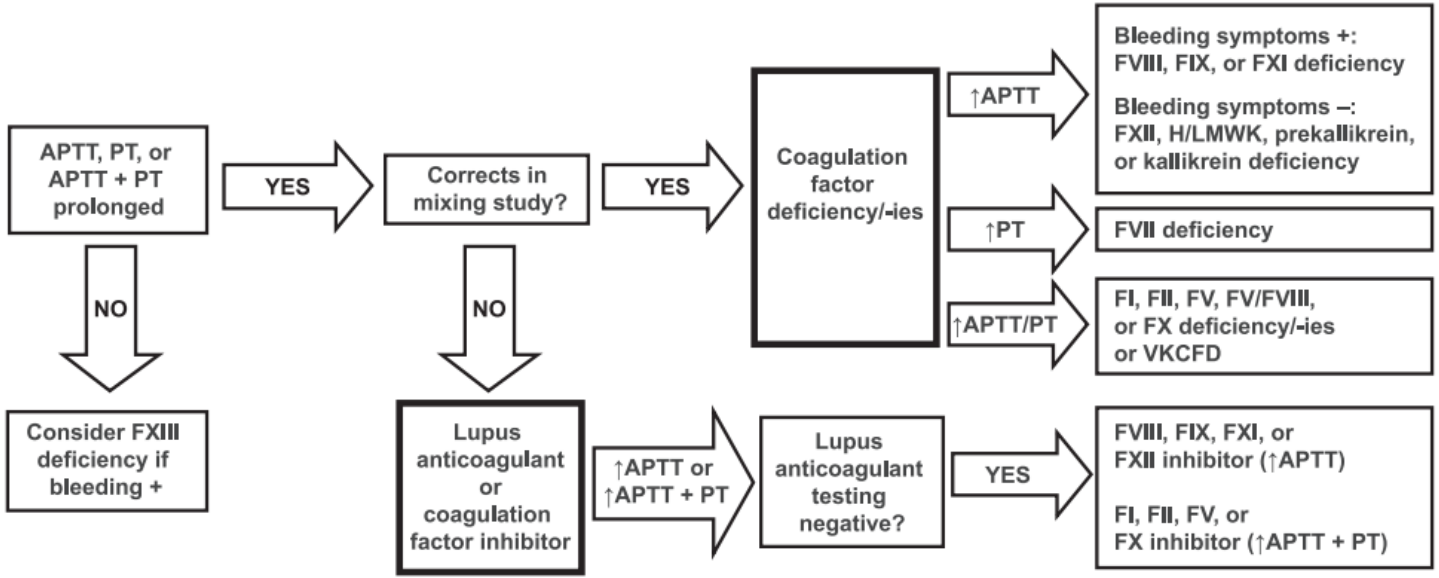


FIGURE 1

Basic process for evaluating coagulation profile abnormalities. If available, a mixing study should be performed to differentiate a coagulation factor deficiency from an inhibitor. The possible factors involved may then be narrowed down on the basis of which coagulation study or studies are abnormal. Note: PT and APTT are normal in FXIII deficiency.[61] H/LMWK, high-/low-molecular-weight kininogen.

TABLE 3: Suggested clinical and laboratory approach to the differential diagnosis of bleeding in newborn babies

	Laboratory investigations			
Health status	**Platelets**	**INR (PT)**	**APTT**	**Possible diagnosis**
Sick	↓	↑	↑	Disseminated intravascular coagulation (usually low factor VIII)
	↓	N	N	Platelet consumption (infection, necrotizing enterocolitis, renal vein thrombosis)
	N	↑	↑	Liver disease, heparinization (usually normal factor VIII)
	N	N	N	Altered vascular integrity (eg, extreme prematurity, severe hypoxia and acidosis
Healthy	↓	N	N	Immune thrombocytopenia, occult infection or thrombosis, abnormal bone marrow function
	N	↑	↑	Hemorrhagic disease of the newborn (vitamin K deficiency)
	N	N	↑	Hemophilia
	N	N	N	Bleeding due to trauma or anatomic abnormalities, qualitative platelet abnormalities

↑ Increased; ↓ Decrease; APTT Activated partial thromboplastin time; DIC Disseminated, intravascular coagulation; INR International normalized ratio; N Normal

TABLE II—*Guidelines for Dosage Requirements in Neonatal Hemostatic Disorders*

Disorder	Transfusion material	Dosage	*In-vivo* half life
Thrombocytopenia	Platelet concentrates	10 ml/kg	1-3 days
Hemorrhagic disease of newborn	FFP+	10-15 ml/kg	Variable
Consumption coagulopathy	FFP, Platelet concentrate	10-15 ml/kg	Variable
Afibrinogenemia	Cryoprecipitates	1 pack/3 kg infant	4-6 days
Factor II deficiency	Prothrombin complex, Concentrates of FFP	FFP 10-15 ml/kg	3-4 days
Factor VII deficiency			4-6 days
Factor X defiency			48-60 hours
Factor IX deficiency			20 hours
Factor VIII deficiency	Cryoprecipitates VIII concentrates	1 cryoprecipitate = 80 units*	12 hours
Factor V deficiency	FFP	10-15 ml /kg	15-24 hours
Factor XI deficiency	FFP	10-15 ml /kg	60 hours
Factor XIII deficiency	FFP	10 ml/ kg	6 days
von Willebrand's disease	Cryoprecipitates	1 pack/3 kg infant	4 hours

Adapted from Hathaway WE(14).

SAMPLING

- CORD BLOOD samples → coagulation testing if there is a suspicion of inherited bleeding disorder
- Venipuncture is preferred
- Heel sticks and arterial draws should be avoided

SAMPLING ERRORS

- Insufficient sample volume and underfilling of collection tubes
- Heparin contamination (sample collected from indwelling catheters or into a preheparinized syringe)
- High hematocrit at birth - required citrate-to-blood ratio of 9 : 1 may not be achieved using standard collection tubes
- Elevated levels of bilirubin or lipids and hemolysis in neonates can interfere with optical density measurements
- Defining appropriate reference ranges for neonates → age-related reference ranges specific for analyzer-reagent combination used in the coagulation laboratory

TABLE 2. Coagulation System Testing of Plasma of Preterm Infants of Different Gestational Ages Obtained at Birth

	GESTATIONAL AGE AT BIRTH		
TEST	**<28 WEEKS**	**28-34 WEEKS**	**>34 WEEKS**
PT: >95th percentile reference interval	>21 sec	>21 sec	>16 sec
aPTT: >95th percentile reference interval	>65 sec	>55 sec	>50 sec
Fibrinogen <5th percentile reference interval	<70 mg/dL	<90 mg/dL	<100 mg/dL

Reference intervals for common coagulation tests of preterm infants. (27) The values (<28 wk) apply only to the first day after birth. No coagulation reference intervals are available for infants <28 weeks' gestation after postnatal day 1. (Over the first days, the 95% interval for PT and aPTT declines, while the 5% interval increases for fibrinogen.)
aPTT=activated partial thromboplastin time, PT=prothrombin time.

Christensen R. D., MacQueen B. C., Carroll P. C. and Sola-Visner M. C. Bleeding Problems in Extremely Low BirthWeight Neonates: Quick (and Wintrobe) Thinking Needed. NeoReviews 2016;17;e645

TABLE 3. **Plasma Concentrations of Selected Procoagulants, Anticoagulants, and Fibrinolytic Components***

PROCOAGULANTS	PRETERM DAY 1	PRETERM DAY 30	TERM DAY 1	TERM DAY 30	ADULTS
Fibrinogen (mg/dL)	243 (150-373)	254 (150-414)	283 (167-399)	270 (162-378)	278 (156-400)
Factor V (U/mL)	0.88 (0.41-1.44)	1.02 (0.48-1.56)	0.72 (0.34-1.08)	0.98 (.62-1.34)	1.06 (0.62-1.50)
Factor VIII (U/mL)	1.11 (0.5-2.13)	0.83 (0.21-1.45)	1.00 (0.50-1.78)	0.91 (0.5-1.57)	0.99 (0.50-1.49)
Factor IX (U/mL)	0.35 (0.19-0.65)	0.44 (0.13-0.80)	0.53 (0.15-0.91)	0.51 (0.21-0.81)	1.09 (0.55-1.63)
ANTICOAGULANTS	**PRETERM DAY 1**	**PRETERM DAY 30**	**TERM DAY 1**	**TERM DAY 30**	**ADULTS**
Antithrombin (U/mL)	0.38 (0.14-0.62)	0.59 (0.37-0.81)	0.63 (0.39-0.87)	0.78 (0.48-1.08)	1.05 (0.79-1.31)
α-2 Macroglobulin (U/mL)	1.10 (0.56-1.82)	1.38 (0.72-2.04)	1.39 (0.95-1.83)	1.50 (1.06-1.94)	0.86 (0.52-1.20)
Protein C (U/mL)	0.28 (0.12-0.44)	0.37 (0.15-0.59)	0.35 (0.17-0.53)	0.43 (0.21-0.65)	0.96 (0.06-1.24)
Protein S (U/mL)	0.26 (0.14-0.38)	0.56 (0.22-0.90)	0.36 (0.12-0.60)	0.63 (0.33-0.93)	0.92 (0.60-1.24)
FIBRINOLYTICS	**PRETERM DAY 1**	**PRETERM DAY 30**	**TERM DAY 1**	**TERM DAY 30**	**ADULTS**
Plasminogen (U/mL)	0.51 (0.33-0.74)	0.54 (0.32-0.75)	0.58 (0.37-0.79)	0.59 (0.38-0.80)	1.00 (0.74-1.26)
Tissue plasminogen activator (ng/dL)	8.48 (3.00-16.70)	4.13 (2.00-7.79)	9.60 (5.00-18.9)	4.10 (1.00-6.00)	4.9 (1.40-8.40)
α-2 Antiplasmin (U/mL)	0.78 (0.40-1.16)	0.89 (0.55-1.23)	0.85 (0.55-1.15)	1.00 (0.76-1.24)	1.20 (0.68-1.36)
Plasminogen activator inhibitor (U/mL)	5.4 (0.00-12.20)	4.30 (0.00-11.8)	6.4 (2.00-15.1)	3.40 (0.00-8.80)	3.6 (0.00-11.0)

**Obtained from blood of preterm neonates (30-36 weeks' gestation) on days 1 and 10, term neonates on days 1 and 30, and adults. (32)(33) Values are mean and the 5th to 95th percentile references.*

Christensen R. D., MacQueen B. C., Carroll P. C. and Sola-Visner M. C. Bleeding Problems in Extremely Low BirthWeight Neonates: Quick (and Wintrobe) Thinking Needed. NeoReviews 2016;17;e645

Safe Routine Newborn Care

- Avoid i.m Vitamin K
- If unavoidable- 27gauge needle i.m with 5 mins direct pressure.
- Oral Vitamin K- 2 mg at birth, then at 1 week and 4 weeks.
- Avoid unnecessary pricks
- Immunization and newborn screening to be done but with similar precautions.

Emergent management if any acute bleed

- Follow **FACTOR FIRST PRINICIPLE**
- **Dosing – 0.5×body weight × desired increase in factor**
- **Intracranial bleeds or major bleeds- 100%**
- **Minor bleeds- 40-50%**
- No role of FFP, Desmopressin.
- Tranexamic acid- for minor bleeds , as an adjunct for surgeries.

TAKE HOME POINTS

- Neonates are in a continuous state of developmental hemostasis.
- Bleeding in neonates can be challenging to diagnose and treat.
- With proper history, systematic evaluation, appropriate diagnosis can be made and treatment can be initiated.
- Initially, treatment is often supportive, but once a diagnosis is made, it can and should be tailored to specific etiologies.