Approach to an Anemic Neonate

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INTRODUCTION:

- Newborns are vulnerable to anemia and the problem itself is complex because of the distinctive nature of the hematopoiesis in fetal and neonatal period.Clinical manifestation may be asymptomatic to an acute life-threatening event. It may lead to delayed brain maturation, tissue hypoxia, and stunted growth(1).

- **Definition- Anemia in newborn is defined ashematocrit or haemoglobin level below the fifth percentile lower reference interval for gestational and postnatal age (Fig 1& 2)** (2).

- The process of haematopoiesis begins in the intrauterine life, sequentially in the yolk sac(3rd weekof gestation) followed by liver (11-12 weeks),and then bone marrow (30 weeks)& at birth, marrow erythropoiesis is major site for blood cells production(3).

- At birth the haemoglobin levels is 14.9-23.7 g/dl in term and 19.1-22.1 g/dl in preterm babies. It rapidly falls (physiological nadir) to 9.5-11 g/dl by 9-11 weeks of postnatal period in term babies and 6.5-9 g/dl by 4-8 weeks in preterm babies(4). After reaching this nadir, the infant's marrow starts its erythropoiesis.

- Anemia of Prematurity is an accentuation of normal physiological anemia and is defined as anemia in a preterm baby <32 weeks of gestation(5).Preterm babies are most vulnerable, because the early gestational age itself causes more pronounced decrease in postanatal haemoglobinand additional factors like poor general condition, reduced life span of RBC (35-40 days *vs.* 60-70 days of term babies), increased phlebotomy losses, accelerated growth rate, poor iron stores(4). In general, even term neonates with normal haemoglobin at birth would have depleted their iron stores by the time they have doubled their birth weight (6,7).

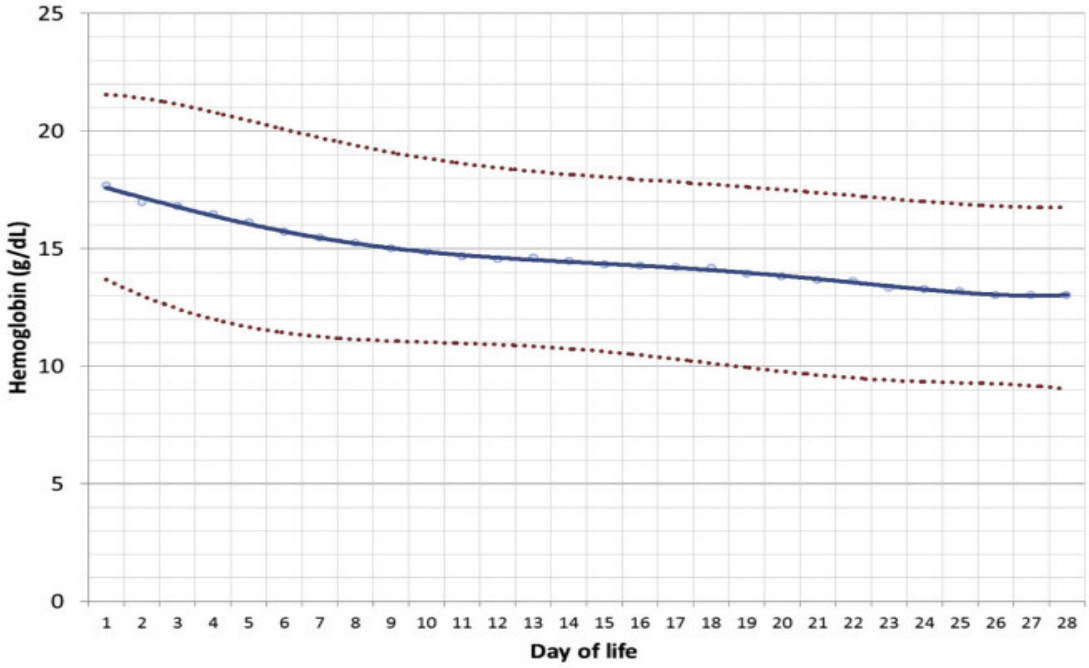


Fig -1. Blood hemoglobin concentration over the first 28 days of life for neonates born at 35 to 42 weeks' gestation.

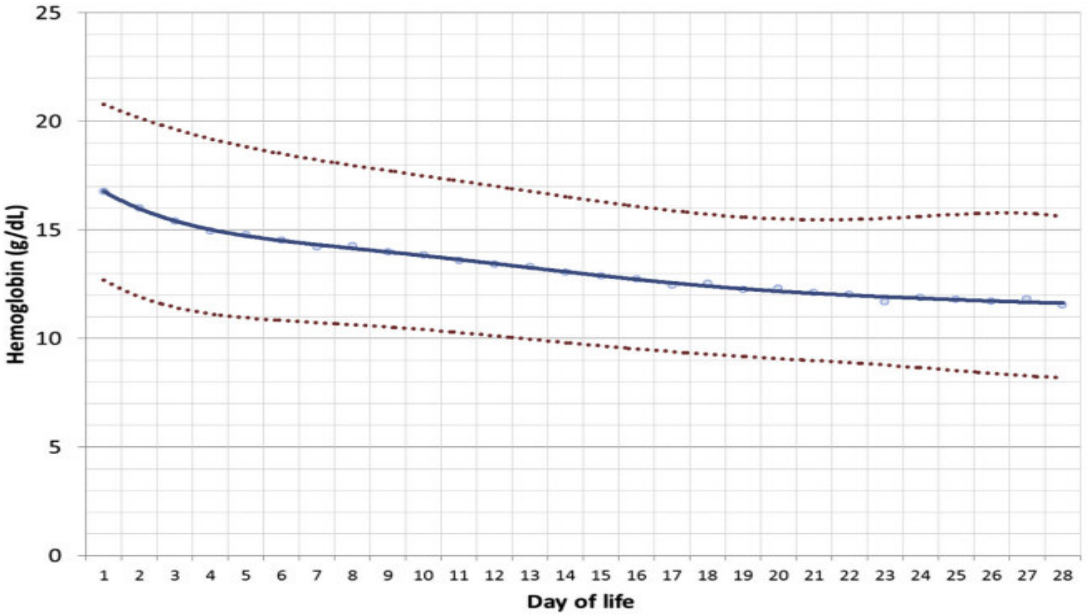


Fig-2. Blood hemoglobin concentration over the first 28 days of life for neonates born at 29 to 34 weeks' gestation

Table 1.0- Causes and Differential diagnosis(5,8)

Serial	Etiology	Causes
1	**Deficient Erythropoesis**	-Anemia of prematurity -Physiological anemia of infancy -Infection (rubella, cytomegalovirus, parvo-virus B19) -Nutritional (deficient iron, folate, vitamin B12) -DiamondeBlackfananemia -Fanconi's anemia -Transient erythroblastopenia of childhood (TEC) -Congenital leukemia -Down syndrome
2	**Enhanced erythrocyte destruction (hemolysis)**	**Hereditary Disorders** -Membrane Defects (spherocycytosis, elliptocytosis etc.) -Enzyme defects (Glucose 6-phosphate dehydrogenase deficiency, Pyruvate kinase deficiency, etc.) -Structural defects (alpha and gamma thalassemia) **Immune Disorders** -ABO incompatibility -Rh incompatibility -Minor blood group incompatibility (kell, kidd, Duffy etc) -Maternal autoimmune diseases (congenital lupus erythematosus) -Drug-induced hemolyticanemia **Acquired** -Sepsis -Disseminated intravascular coagulation -Vitamin E deficiency
3	**Anemia due to blood loss (hemorrhage)**	**Prenatal** -Twin-twin transfusion -Fetal-maternal hemorrhage -Fetal-placental hemorrhage **Perinatal** Vasa previa,Placentaprevia,Abruptio placenta Rupture of umbilical cord,Hematoma,Aneurysm Nuchal cord **Postnatal** Subgalealbleed,Intracranial bleed Intraventricular bleed,Pulmonary bleed Cephalhematoma,Trauma to organ(liver, spleen, adrenal) Iatrogenic (phlebotomy loss)

APPROACH TO DIAGNOSIS

Diagnostic approach to anemia in newborn should include a focussed medical history followed by stepwise investigations.

Focussed medical history –

- Maternal history

  1.Blood group: ABO, Rh incompatibility

  2.Complete blood count: anemia, blood loss, thrombocytopenia

  3. Antibody screening: Systemic lupus erythematosus (congenial lupus)

  4. Bleeding disorders

  5. Infections (TORCH)

  6. H/O trauma

  7. H/O maternal bleed- placenta previa, cord prolapse(acute blood loss)

  8. Evidence of fetal distress

  9. Mode of delivery (Instrumental)

- Family history(Anemia, Cholelithiasis, Splenectomy) –

  1. Autosomal recessive- Fanconi's anemia, PK deficiency,
  2. Autosomal dominant- Hereditary Spherocytosis (HS), Hereditary Elliptocytosis (HE)
  3. X linked – G6PD deficiency

- Newbornhistory–

  1.Ethnicity/Race (Thalassemia, G6PD)

  2.Sex (G6PD)

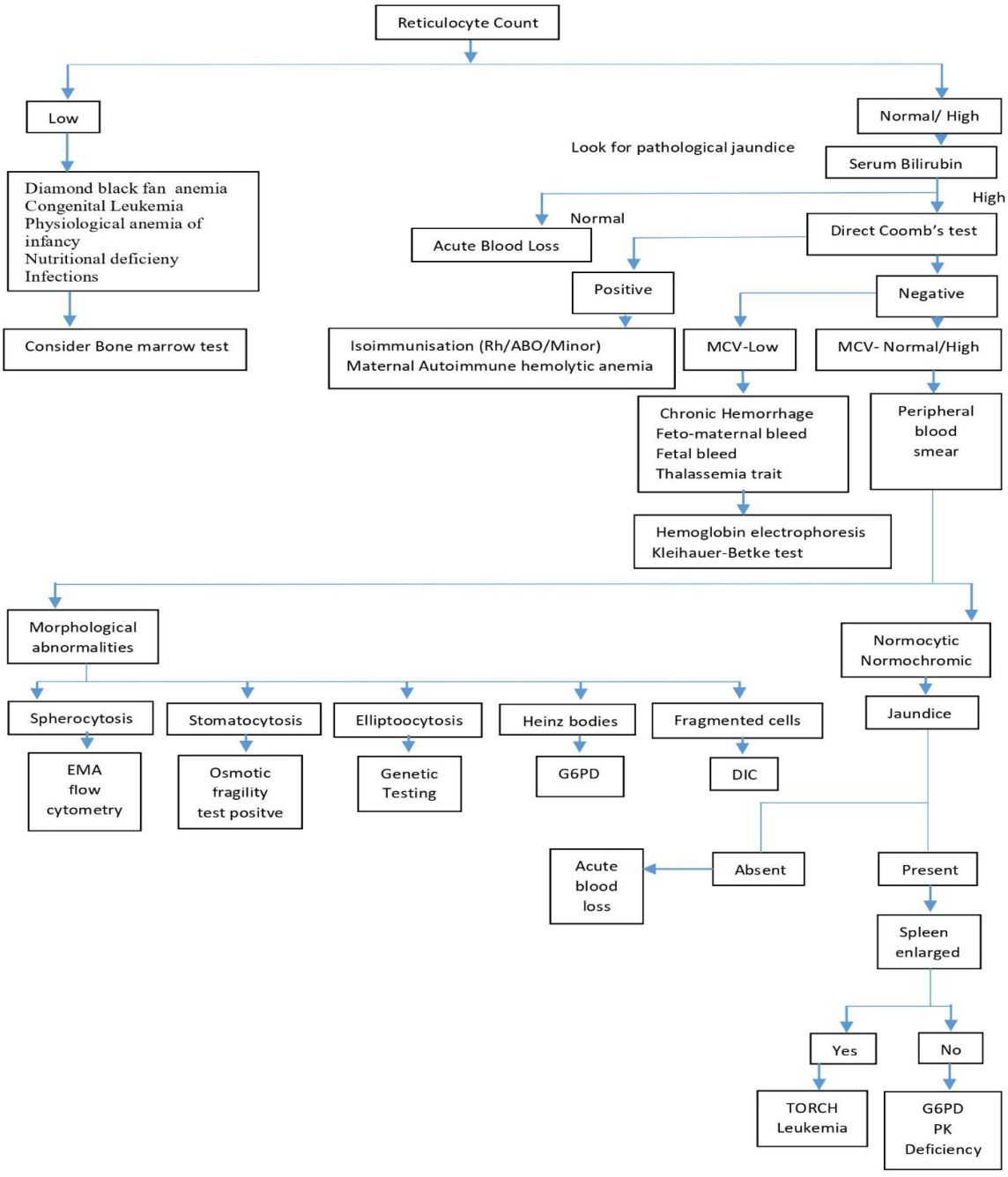
  3.Age at presentation

  a. At Birth – Blood loss, Alloimmunisation.

  b. After 24 Hours- Internal bleed

  c. Weeks after birth- Anemia of prematurity, Hypoplastic anemia, RBC structural defects

Fig 3 : Stepwise Laboratory Evaluation



TREATMENT

A. PROPHYLAXIS

In Premature infants: the aim should be to ward off orameliorate the anemia of prematurity. The following factors should be considered:

a. **Delayed Cord Clamping** : In preterm infants, delayed clamping appears to reduce the risk of intraventricular hemorrhage and the need for neonatal transfusions(9). Delayed umbilical cord clamping (not earlier than 1 min after birth) is recommended for improved maternal and infant health and nutrition outcomes.(10)

b. **Iron** supplementation should be started between 4 and 6 weeks of age once full enteral feeding is achieved(11). Iron deficiency as well as iron overload is a crucial issue in preterms, as excess exogenous iron can result into oxidative damage(12). It is still unclear whether iron supplementation in preterm and low birth weight infants has long-term benefits in terms of neurodevelopmental outcome and growth.

Table2.0- Iron supplementation for preterm neonates

Gestational age	Birth weight	Dose of elemental iron	When to start	To be continued till period
<32weeks	<1500g	2mg/kg/day	At 4weeks	2 years of age
>32 weeks	1500-2499g	2mg/kg/day	At 4weeks	2 years of age

c. **Vitamin E** (5 to 25 IU of water-soluble form) should be added as supplement daily until the baby is 38 to 40 weeks' postconceptional age(11).

d. **Recombinant human erythropoietin** (**rh-EPO**) most of the studies have shown that erythropoietin is of limited benefit in reducing the number or volume of transfusions.Increased risk for retinopathy of prematurity(ROP) has been reported in some studies(13–16). At present, EPO is not routinely used as prophylaxis for anemia.

e. Definitive measures should be taken **to decrease phlebotomy losses**. These include cord blood sampling for immediate postnatal labs (e.g. type and cross-match), microsampling, batching and judicious use of laboratory tests, use of point-of-care laboratory testing devices, and prompt removal of central arterial and venous catheters providing easy access to blood(11).

f. **Regular follow up and clinical examination**.

B. TRANSFUSION GUIDELINES:

Table3.0- Transfusion guidelines for preterm neonates(preferably <32weeks (17)

Day of Life	Suggested transfusion threshold Hb(g/dl)		
	Ventilated	On oxygen/CPAP/NIPPV	Off Oxygen
1st 24hour	<12	<12	<10
Day 2 to 7	<12	<10	<10
Day 8 to 14	<10	<8.5-9.5	<7.5
Day 15 onward	<10	<8.5	<7.5

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Table4.0- Liberal vs Restrictive Transfusion Thresholds in Extremely Low-Birth-Weight Infants (18)

	Liberal Red Blood Cell Transfusion Thresholds		Restrictive Red Blood Cell Transfusion Thresholds	
Postnatal Age	State of Health		State of Health	
	Critical	Non Critical	Critical	Non Critical
Till 7 days (After Birth)	<8.5 mmol/l (13.6 g/dl)	<7.2 mmol/l (11.6 g/dl)	<7.0 mmol/l (11 g/dl)	<5.8 mmol/l (9.3 g/dl)
8-21 days	<7.6 mmol/l (12 g/dl)	<6.4 mmol/l (10.3 g/dl)	<6.2 mmol/l (10 g/dl)	<5 mmol/l (8 g/dl)
>21 days	<7.0 mmol/l (11 g/dl)	<5.8 mmol/l (9.3 g/dl)	<5.6 mmol/l (9 g/dl)	<4.3 mmol/l (7 g/dl)

Table3 shows guideline published in 2019, Effects of Liberal vs Restrictive Transfusion Thresholds on Survival and Neurocognitive Outcomes in Extremely Low-Birth-Weight Infants: The ETTNO Randomized Clinical Trial.Itis a multicentre trial conducted in Europe.However,there is no significant difference in the combined outcome of death or significant morbidity at discharge on using low versus high hemoglobin threshold for blood transfusion in VLBW neonates.Therefore, restrictive transfusion policy is recommended to be followed.

Table5.0- Transfusion threshold for term neonates(17)

Morbidity	Hb level(g/dl)
Severe pulmonary disease	<12
Moderate pulmonary disease	<10
Severe cardiac disease	<12
Major surgery	<10
Symptomatic anemia	<7

C. **Amount of transfusion to be given:** it is recommended to transfuse 10-15ml/kg packed red blood cell and the rate should not exceed 5ml/kg/hour.(19)

SUMMARY:

- Anemia in newborn is defined as hematocrit or haemoglobin level below the fifth percentile lower reference interval for gestational and postnatal age
- At birth the haemoglobin levels is 14.9-23.7 g/dl in term and 19.1-22.1 g/dl in preterm babies. Physiological nadir reached to 9.5-11 g/dl by 9-11 weeks of postnatal period in term babies and 6.5-9 g/dl by 4-8 weeks in preterm babies
- Anemia of Prematurity is an accentuation of normal physiological anemia and is defined as anemia in a preterm baby <32 weeks of gestation
- Phlebotomy loss is crucial in babies admitted in neonatal intensive care units, which needs consideration.
- Delayed umbilical cord clamping (not earlier than 1 min after birth) is recommended for improved maternal and infant health and nutrition outcomes
- Iron, folate, vitamin B12 and Vitamin E supplementation should be started once enteral feeding has been established.

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