33 Polycythemia

Polycythemia – elevated hematocrit – is associated with hyperviscosity of blood. As the blood viscosity increases, there is impairment of tissue oxygenation and perfusion and tendency to form microthrombi. Significant damage may occur if these events occur in the cerebral cortex, kidneys and adrenal glands. Hence, polycythemia requires urgent diagnosis and prompt management.

Viscosity of blood is directly proportional to hematocrit and plasma viscosity, and inversely proportional to deformability of red blood cells. Symptoms of hypoperfusion correlate better with viscosity as compared to hematocrit. Viscosity is, however, difficult to measure at the bedside. Hyperviscosity is therefore suspected in the presence of an abnormally high hematocrit with or without suggestive symptoms.

Relationship between viscosity and hematocrit is almost linear up to a hematocrit of 65% and exponential thereafter.[1,2] The polycythemia-hyperviscocity syndrome is thus usually confined to infants with hematocrits of more than 65%; it is very rare with hematocritsof <60%.

Definition

Diagnosis of polycythemia is made in the presence of a venous hematocrit more than 65% or a venous hemoglobin concentration of more than 22 gm/dL. Hyperviscosity is defined as a viscosity greater than 14.6 centipoise at a shear rate of 11.5 per second.[3]

Incidence

Incidence of polycythemia varies from 1.5% to 4% of live births.[4,5] The incidence was found to be 0.7% of live births in the last 7 years in our unit. Incidence is higher in small-for-gestational age (SGA) and large-for-gestational age (LGA) infants. About 15% of term SGA infants develop polycythemia as compared to 2% of term AGA infants.[6]

Neonates born at high altitude also have a higher incidence of polycythemia.[1] Maternal smoking is an important risk factor for polycythemia.[7] Term neonates born to mothers engaged in smoking during pregnancy are 2.5 times more likely to require a partial exchange transfusion for polycythemia than the counterparts of non-smoker mothers.[7] Infants born by cesarean section have a lower hematocrit values than those delivered vaginally.[8] Infants subjected to delayed cord clamping also carry higher risk of asymptomatic polycythemia.[9]

Physiological changes in postnatal life

Significant changes take place in the hematocrit from birth through the first 24 to 48 hr of life. The hematocrit peaks at around 2 hr of age and values up to 71% may be normal at this age.[10-11] It gradually declines to 68% by 6 hr and usually stabilizes by 12 to 24 hr. The initial rise in hematocrit is related to a transudation of fluid from the intravascular space.

Etiology of polycythemia (Table 33.1)[12]

Table 33.1: Etiological factors for polycythemia

Increased erythropoiesis	Secondary to transfusions
1. Intrauterine hypoxia 1. Placental insufficiency 2. Small-for-gestational-age infant 3. Post-maturity 4. Toxemia of pregnancy 5. Drugs (e.g. propranolol) 6. Severe maternal heart disease 7. Maternal smoking 2. Maternal diabetes 3. Neonatal hyperthyroidism or hypothyroidism 4. Congenital adrenal hyperplasia 5. Chromosome abnormalities 1. Trisomy 13 2. Trisomy 18 3. Trisomy 21 (Down syndrome) 6. Beckwith Wiedemann Syndrome	1. Delayed cord clamping 2. Maternal to fetal transfusion 3. Twin-to-twin transfusion

Clinical features

Polycythemia can result in a wide range of symptoms involving several organ-systems (Panel 1). About 50% of neonates with polycythemia develop one or more symptoms. However, most of these symptoms are non-specific, and may be related to the underlying conditions rather than due to polycythemia per se.

Panel 1: Clinical features ascribed to polycythemia and hyperviscosity

Central nervous system
- Early: Hypotonia and sleepiness, irritability, jitteriness, seizures and infarcts
- Late: motor deficits, lower achievement and IQ scores

Metabolism
- Hypoglycemia
- Jaundice
- Hypocalcemia

Heart and lungs
- Tachycardia, tachypnea, respiratory distress
- Cyanosis, plethora
- Chest X-ray: cardiomegaly, pulmonary plethora
- Echocardiography: increased pulmonary resistance, decreased cardiac output

Gastrointestinal tract
- Poor suck, vomiting
- Feed intolerance – abdominal distension
- Necrotizing enterocolitis

Kidneys
- Oliguria
- Transient hypertension
- Renal vein thrombosis

Hematology
- Mild thrombocytopenia
- Thrombosis (rare)

Miscellaneous
- Peripheral gangrene
- Priapism
- Testicular infarction

Screening for polycythemia

Screening for polycythemia should be done in certain high-risk groups (Panel 2).

Any infant with clinical features suggestive of polycythemia should be investigated for the same.

Panel 2: Screening for polycythemia

Eligible candidates

(a) Small for gestational age (SGA)
(b) Infants of diabetic mothers (IDM)
(c) Large for gestational age (LGA)
(d) Mono-chorionic twins, especially the larger twin
(e) Infants with morphological features of intrauterine growth restriction such as three or more loose folds of skin around the buttock and thighs, loss of subcutaneous fat, difference of head circumference and chest circumference >3 cm

Schedule

2 hr of life; if high, repeat at 6 hr, 12 hr, 24 hr and 48 hr

Method

Centrifuge venous blood in heparinized capillaries for 3 to 5 min @ 10000 to 15000 rpm

Blood sample for hematocrit can be obtained by either heel-prick (capillary hematocrit) or by venipuncture (venous hematocrit). Capillary hematocrit measurements are, however, unreliable and highly subject to variations in blood flow. They are significantly higher than venous hematocrits. This difference is even more apparent in infants receiving large placental transfusion.[13]

Practice tip

Capillary samples may be used for screening but all high values should be confirmed by a venous sample for the diagnosis of polycythemia.

Methods of hematocrit determination

Two methods are available:

1. *Automated hematology analyzer*: This calculates the hematocrit from a direct measurement of mean cell volume and hemoglobin.
2. *Micro-centrifuge*: Blood is collected in heparinized micro-capillaries (110 mm length and 1-2 mm internal diameter) and centrifuged at 10,000 to 15,000 rotations per minute (rpm) for

3-5 minutes. Plasma separates and the packed cell volume is measured to give the hematocrit.

An automated analyzer gives lower values as compared to hematocrits measured by the centrifugation method.[14] Most of the reported data on polycythemia is on centrifuged hematocrits.

Management

Before the diagnosis of polycythemia is considered, it is mandatory to exclude dehydration. If the birth weight is known, re-weighing the baby and looking for excessive weight loss (more than 10% to 15%) would help in the diagnosis of dehydration. Dehydration, if present, should be corrected by increasing fluid/feed intake. The hematocrit should be measured again after correction of dehydration. Once a diagnosis of polycythemia is made, associated metabolic problems including hypoglycemia should be excluded.

Management of polycythemia is dependent upon two factors (Figure 33.1):

1. Presence of symptoms suggestive of polycythemia
2. Absolute value of hematocrit

(a) Symptomatic polycythemia

The definitive treatment for polycythemia is to perform a partial exchange transfusion (PET). PET involves removing some volume of the blood and replacing it with normal saline so as to decrease the hematocrit to a target hematocrit of 55% (Panel 3). Following PET, symptoms like jitteriness may persist for 1-2 days despite the hematocrit being lowered to physiological ranges.

Panel 3: Volume to be exchanged in PET

$$\text{Volume to be exchanged} = \frac{\text{Blood volume}^* \times (\text{observed hematocrit} - \text{desired hematocrit})}{\text{Observed hematocrit}}$$

For example, for a 35 wk gestation newborn weighing 2 kg (assumed blood volume 90 mL/kg) and observed hematocrit of 75% and desired hematocrit of 55%, the amount of blood to be exchanged would be:

=2*90* (75-55/75)

=48 mL of blood to be exchanged with normal saline to bring hematocrit from 75% to 55%

Rule of thumb: Volume of blood to be exchanged is usually 20 mL/kg

**Refer Rawlings Chart[15] for estimating the blood volume; as a rough guide, it is 80-90 mL/kg in term babies and 90-100 mL/kg in preterm babies*

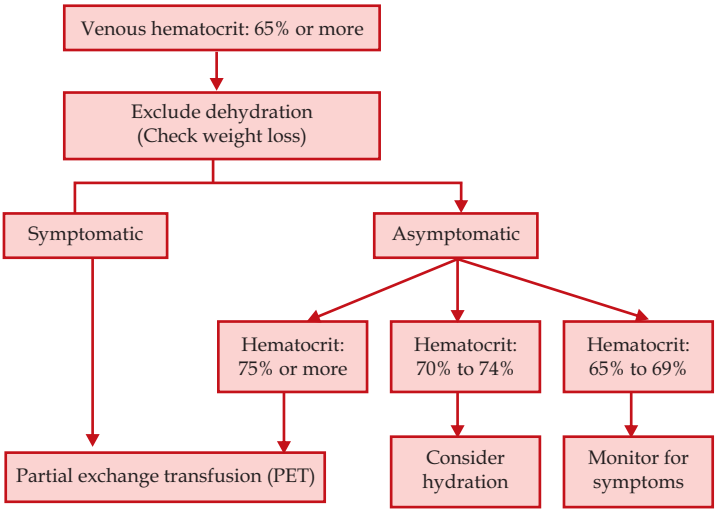

Figure 33. 1: Management algorithm of polycythemia

PET: peripheral vs. umbilical route

PET may be carried out via the peripheral or the central route. In the former, blood is withdrawn from the peripheral arterial line and replaced with saline simultaneously via a peripheral venous line. In the central route, blood is withdrawn from the umbilical venous catheter while saline is replaced by a peripheral vein. Alternatively, in central route, the umbilical venous catheter may be used for both withdrawal of blood and replacement of saline (pull and push technique, similar to double volume exchange transfusion for severe jaundice), or the blood is withdrawn from umbilical arterial line and saline replaced from umbilical venous line.

One prospective study found increased infection rate without any increased risk of NEC following partial exchange using umbilical vein.[16] Though there is no concrete evidence against use of umbilical vein for partial exchange, peripheral anerial route seems to be a safer option.

PET: choice of exchange fluid

Crystalloids such as normal saline (NS) or Ringer's lactate (RL) are preferred over colloids, because they are less expensive and are easily available. Crystalloids produce nearly comparable reduction in hematocrit as colloids (Panel 4),[17,18] and do not have the risk of transfusion associated infections. Moreover, adult plasma has been shown to increase the blood viscosity when mixed with fetal erythrocytes.

Panel 4: Choice of exchange fluid: What is the evidence?

A systematic review determined efficacy of crystalloid versus colloid solutions to identify the best fluid for PET[17]:

- Clinically unimportant difference in hematocrit favoring colloids than crystalloids:
  - o at 2-6 h: 2.3% (95% CI 1.3% to 3.3%)
  - o at 24 h: 1.7% (95% CI 0.8% to 2.7%)
- This difference was more significant when NS was compared to plasma but absent when compared with 5% albumin.
- No side effects of using colloids were found

We use only normal saline for partial exchange transfusion.

(b) Asymptomatic polycythemia

The line of management in infants with asymptomatic polycythemia depends upon their hematocrit values.

i. Hematocrit 75% or more: These infants are usually managed with PET.

ii. Hematocrit between 70% and 74%: Conservative management with hydration is tried in these infants. An extra fluid/feeds of 20 mL/kg may be added to the daily fluid requirements. The additional fluid may be ensured by either enteral (supervised feeding) or parenteral route (IV fluids). Rationale for this therapy is that additional fluids result in hemodilution there by reducing the blood viscosity.

iii. Hematocrit between 65% and 69%: These infants only need monitoring for symptoms of polycythemia and re-estimation of hematocrit. Further management depends upon the repeat hematocrit values. The RCT on fluid supplementation (20-25 mL/kg over 6-8 hours) vs. no

fluid supplementation in 55 late preterm and term neonates with asymptomatic polycythemia (hematocrit: 65% to 70%) found no significant difference in the need for partial exchange transfusion between the two groups.[19]

Evidence for management of polycythemia

PET reverses the physiological abnormalities associated with the polycythemia–hyperviscocity syndrome. It improves capillary perfusion, cerebral blood flow and cardiac function. However, there is very little data to suggest that PET improves long-term outcomes in patients with polycythemia. The Cochrane review (2010) concluded that there are no proven clinically significant short-or long-term benefits of PET in polycythemic infants who are clinically well or who have minor symptoms related to hyperviscosity. Also, PET may increase the risk of NEC (Panel 5).[20]

Panel 5: Partial exchange transfusion for polycythemia: What is the evidence?

A Cochrane review (2010)[20] on this issue showed:

- No effect on neonatal mortality (one study; RR 5.23, 95% CI 0.66, 41.26).
- No difference in developmental delay (4 low quality studies; RR 1.45, 95% CI 0.83 to 2.54)
- Increased risk of NEC in infants receiving PET (2 studies; RR 11.18, 95% CI 1.49, 83.64)
- No differences in short-term complications including hypoglycemia (two studies) and thrombocytopenia (one study)

However, the studies included in the review were of low quality; also, most surviving infants were not assessed for developmental outcomes, and therefore, the true risks and benefits of PET are unclear. The study by Iris et al showed that restrictive management of polycythemia does not increase short term complications.[21]

Given the uncertainty regarding the long-term outcomes, it is preferable to restrict PET in symptomatic infants with hematocrit of >65% and in asymptomatic neonates with hematocrit of >75%.

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