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Polycythemia in the Newborn

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ABSTRACT

Polycythemia is defined as a venous hematocrit of over 65%. The hematocrit in a newborn peaks at 2 hours of age and decreases gradually after that. The etiology of polycythemia is related either to intra-uterine hypoxia or secondary to fetal transfusion. The relationship between hematocrit and viscosity is almost linear till 65% and exponential thereafter. Increased viscosity of blood is associated with symptoms of hypo-perfusion. Clinical features related to polycythemia-hyperviscosity syndrome may affect all organ systems and this entity should be screened for in high-risk infants. Polycythemia may or may not be symptomatic and guidelines for management of both the types based on the current evidence are provided in the protocol.
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Polycythemia or an increased hematocrit is associated with hyperviscosity of blood. As the viscosity increases, there is an impairment of tissue oxygenation and perfusion and a tendency to form microthrombi. Significant damage may occur if these events occur in the cerebral cortex, kidneys and adrenal glands. Hence, this condition requires urgent diagnosis and prompt management.

Polycythemia and Hyperviscosity

The viscosity of blood is directly proportional to the hematocrit and plasma viscosity and inversely proportional to the deformability of red blood cells. Relationship between viscosity and hematocrit is almost linear up to a hematocrit of 65% and exponential thereafter.[1,2] The polycythemia-hyperviscocity syndrome is usually confined to infants with hematocrit at high normal or above normal range. It is very rare with hematocrits of less than 60%. In addition to an increase in hematocrit, hyperviscosity might also result from an increase in plasma proteins especially fibrinogen and decreased deformability of fetal erythrocytes.

Symptoms of hypoperfusion correlate better with blood viscosity as compared to the hematocrit.[3] Viscosity however, is difficult to measure. It is measured by Wells-Brookfield cone-plate micro-viscometer. Since instruments to measure viscosity are not readily available in most neonatal intensive care units, hyperviscocity is usually suspected in the presence of suggestive symptoms and/or an abnormally high hematocrit.

Definition

A diagnosis of polycythemia is made in the presence of a venous hematocrit more than 65% or a venous hemoglobin concentration in excess of 22.0 gm/dL. Hematocrit (%) is approximately three times the hemoglobin concentration in gm/dL.

Hyperviscosity is defined as a viscosity greater than 14.6 centipoise at a shear rate of 11. 5 seconds^{-1}.

Incidence

The incidence of polycythemia is 1.5-4% of all live births.[4,5] The incidence is higher among both small for gestational age (SGA) and large for gestational age (LGA) infants. It is 15% among term SGA infants as compared to 2% in term appropriate for gestational age (AGA) infants.[6] Neonates born to mothers at high altitudes also have a higher incidence of polycythemia.[1] Polycythemia is less likely to occur in neonates born at a gestational age less than 34 weeks.[1]

Physiological changes in postnatal life

Significant changes take place in the hematocrit from birth through the first 24 hours of life. The hematocrit peaks at 2 hours of age and values upto 71% may be normal at this age[7,8] It gradually declines to 68% by 6 hrs

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and usually stabilizes by 12 to 24 hours. The initial rise in hematocrit is related to a transudation of fluid out of the intravascular space. There is a significant correlation between cord hematocrit greater than 56% and a venous hematocrit > 70% at 2 hours of age.[7]

Etiology of polycythemia

Polycythemia in neonates may be a compensatory mechanism for intra-uterine hypoxia or secondary to fetal transfusions (Table 1).

Table 1. Causes of Polycythemia

Secondary to transfusion
Delayed cord clamping
Holding the baby below the level of introitus
Twin to twin transfusion
Maternal fetal transfusion
Perinatal asphyxia
Secondary to intrauterine hypoxia
Intra-uterine growth restriction
Gestational hypertension
Maternal diabetes (insulin dependent & gestational)
Maternal smoking
Maternal cyanotic heart disease
Post maturity
Fetal causes
Trisomy 13,18,21
Hypothyroidism, Thyrotoxicosis
Congenital adrenal hyperplasia
Beckwith Weidemann syndrome

Fetal transfusions: Polycythemia secondary to fetal transfusions may occur due to twin to twin transfusion, maternal-fetal transfusion, or delayed cord clamping. Delayed cord clamping is defined as clamping more than 3 minutes after the delivery of baby. This has been associated with a 30% increase in blood volume as compared to neonates with early clamping (within 30 seconds of delivery) .[9,10] Possible ways of avoiding polycythemia include early cord clamping and holding the baby at the level of the introitus at the time of delivery to minimize maternal-fetal transfusion.

Intra-uterine hypoxia: The second reason for polycythemia is increased RBC production as a compensatory mechanism for intra-uterine hypoxia. Conditions associated with intra-uterine hypoxia include intrauterine growth restriction (IUGR), gestational hypertension, maternal diabetes mellitus, maternal smoking, maternal cyanotic heart disease, infants with perinatal asphyxia and post-mature deliveries. Increased number of nucleated red blood cells in IUGR babies is a marker of intra-uterine hypoxia. The incidence of polycythemia increases with increasing severity of growth restriction.[11] In severely growth restricted fetuses, a hematological syndrome of polycythemia, thrombocytopenia, leukopenia and increased numbers of nucleated red blood cells has been described.[12] Infants of diabetic mothers also have a high incidence of polycythemia. Polycythemia in these infants correlates with macrosomia and neonatal hypoglycemia.

Fetal causes: Polycythemia may also occur secondary to fetal causes. (Table 1)

Dehydration as a cause of increased hematocrit should always be ruled out before diagnosing polycythemia.

SCREENING FOR POLYCYTHEMIA

Screening for polycythemia should be done in certain high-risk groups (Table 2). We recommend screening in high-risk neonates at 2 hours of age. A normal value at 2 hours of age (hematocrit <65%) does not merit any further screening unless the infant is symptomatic. Hematocrit values >65% at 2 hours of age merit repeat screening at 12 and 24 hours. Polycythemia is diagnosed when venous hematocrit is >65%. Any infant with clinical features suggestive of polycythemia should be examined for polycythemia.

Table 2. Indications for Screening for Polycythemia

(a)	Small for gestational age (SGA) infants
(b)	Infants of diabetic mothers (IDM)
(c)	Large for gestational age (LGA) infants
(d)	Monochorionic twins especially the larger twin
(e)	Infants with morphological features of growth restriction.

Capillary *vs* venous hematocrit

Capillary hematocrit measurements are unreliable and highly subject to variations in blood flow. Capillary hematocrits are significantly higher than venous hematocrits. This difference is even more apparent in infants receiving large placental transfusion.[13] 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 analysis

The two available methods are
Automated hematology analyzer: This calculates the hematocrit from a direct measurement of mean cell volume and the hemoglobin.

Micro-centrifuge: Blood is collected in heparinized micro-capillaries (110mm length and 1-2mm internal diameter) and centrifuged at 10,000-15,000 rounds 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.

Clinical features

Polycythemia can result in a wide range of symptoms

involving several organ systems (Table 3). 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*.

TREATMENT

Before a 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 would help in the diagnosis of dehydration. If this is present, it should be corrected by increasing fluid intake. Hematocrit should be measured once again after correction of dehydration. Once a diagnosis of polycythemia is made, associated metabolic problems including hypoglycemia should be excluded. Two modes of treatment have been described for polycythemia.

(a) Conservative management with hydration: This mode of therapy may be tried in asymptomatic polycythemia when the hematocrit reaches 70 to 75%. An extra fluid aliquot of 20 mL/Kg may be added to the daily fluid requirements. Extra fluid intake may be ensured either by the enteral route (supervised feeding) or parenteral route (IV). The rationale for this therapy is hemo-dilution and the resultant decrease in viscosity. However, liberal and extra fluid therapy may be associated with problems especially in preterm infants. Hence, conservative management by using extra fluids should be reserved for hemodynamically stable neonates with asymptomatic polycythemia.

(b) *Partial exchange transfusion (PET):* The definitive treatment for polycythemia is a partial exchange transfusion. Indications for PET include:

- Presence of symptoms suggestive of polycythemia/ hyperviscosity
- Hematocrit >75% in an asymptomatic infant.

A partial exchange transfusion (PET) aims to decrease the hematocrit to a target packed cell volume of 55%. Following partial exchange transfusion, symptoms like jitteriness may persist for 1-2 days despite the hematocrit being lowered to physiological ranges.

The volume of blood to be exchanged is given by the formula shown in the box.

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

*Blood volume is estimated to be 80-90 mL/Kg in term babies and 90-100 mL/Kg in preterm babies.

As a rough guide, the volume of blood to be exchanged is usually 20 mL/Kg.

Fluids to be used for PET

(i) Crystalloids: normal saline, ringer lactate

(ii) Colloids: fresh frozen plasma, 5% albumin

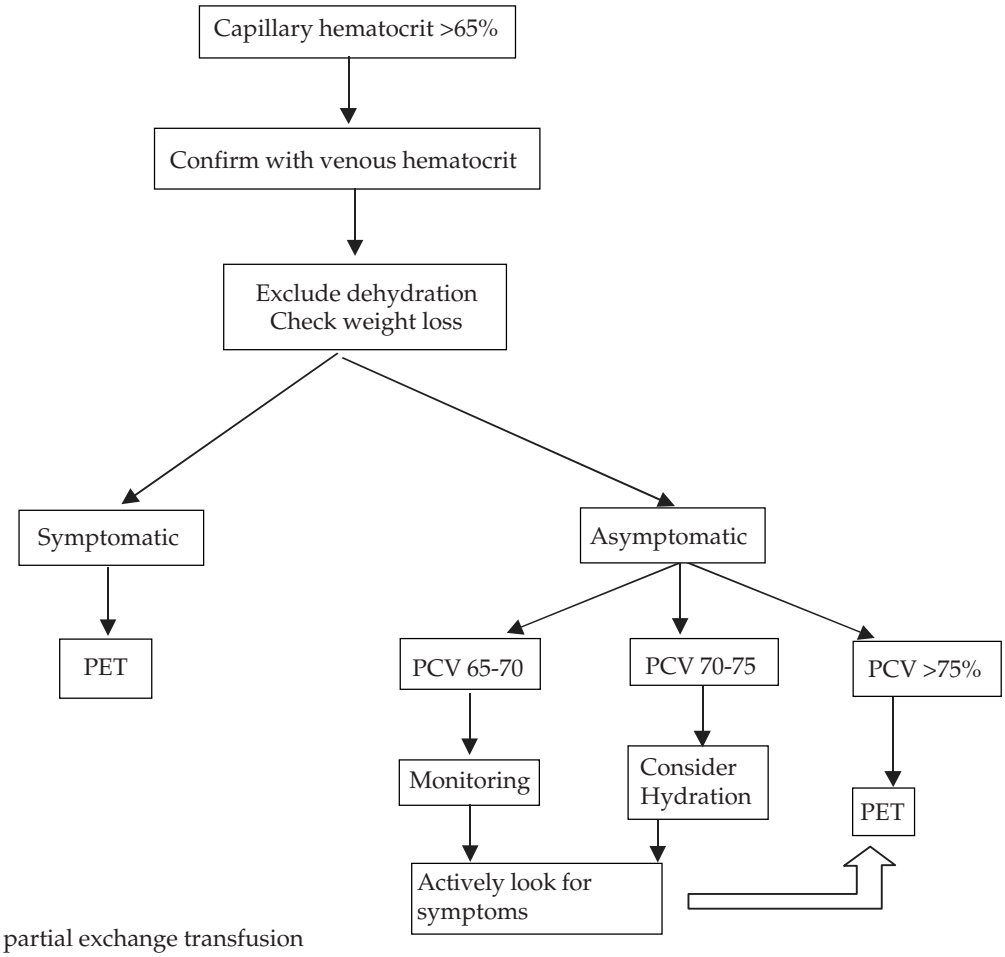
Cystalloids are preferred because they are economical and easily available, produce a similar reduction in hematocrit as colloids,[15,16] and do not carry a risk of transfusion associated infections (*e.g.*, HIV, Hepatitis B, C and CMV). Additionally, adult plasma has been shown to increase the blood viscosity when mixed with fetal erythrocytes. We use normal saline for partial exchange transfusion.

Peripheral vs umbilical route

A partial exchange transfusion may be carried out *via* the peripheral route or the central route. A peripheral route avoids umbilical vessel cannulation and is done by using a peripheral arterial and venous line. Blood is withdrawn from the arterial line and replaced simultaneously via the venous line. A central route requires cannulation of the umbilical vein. The umbilical venous catheter may be used for withdrawing blood while the same amount of saline is replaced through a peripheral vein. Alternatively the umbilical venous catheter may be used both for withdrawal of blood and replacement with saline. A recent systematic review has shown that the partial exchange transfusion through umbilical route may be

Table 3. Clinical Features Ascribed to Polycythemia and Hyperviscosity

Central nervous system
Early effects: Hypotonia and sleepiness, irritability and jitteriness
Neurodevelopment: motor deficits, lower achievement and IQ scores
Metabolism
Hypoglycemia
Jaundice
Hypocalcemia
Heart and lungs
Tachycardia, tachypnea, respiratory distress
Cyanosis, plethora
Chest radiography: cardiomegaly, pulmonary plethora
Echocardiography: increased pulmonary resistance, decreased cardiac output
Gastrointestinal tract
Poor suck, vomiting
Necrotizing enterocolitis
Kidneys
Oliguria (depending on blood volume)
Hematology
Mild thrombocytopenia
Thrombosis (rare)
Miscellaneous
Peripheral gangrene
Priapism
Testicular infarction



PET: partial exchange transfusion

Fig. 1. Algorithm for management of polycythemia

associated with increased risk of necrotizing enterocolitis.[17]

Long term outcome with polycythemia

A partial exchange transfusion 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 outcome in patients with polycythemia. Bada *et al* have failed to show any beneficial effect on long term outcome with partial exchange transfusion in neonates with asymptomatic polycythemia.[6] Similarly studies by Black *et al*[11,18] and Goldberg *et al*[12] also failed to demonstrate improvement in long term outcome with the use of exchange transfusions. The systematic review by Dempsey *et al* also reinforces this finding.[17] It is possible that the underlying etiology of polycythemia is the important determinant of ultimate outcome than treatment *per se*.

However, definitive data on long-term outcome with treatment is still unavailable in infants with symptomatic polycythemia and in asymptomatic infants with hematocrit >70-75 %. Therefore, it may be better to do a partial exchange transfusion or consider plasma expansion with additional fluids depending on the presence or absence of symptoms in these group of neonates. We perform partial exchange transfusion at hematocrit values of 65% and at 75% for symptomatic and asymptomatic infants respectively.

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