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Blood sampling in very low birth weight infants receiving different levels of intensive care

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Abstract. Sixty very low birth weight infants (birth weight 560–1450 g) were studied during the first 28 days of life. The infants were classified as group A ($n = 19$ infants who never required ventilator support), group B ($n = 20$ infants mechanically ventilated for minor respiratory problems), and group C ($n = 21$ infants ventilated for respiratory distress syndrome). Diagnostic blood sampling was measured, infants were checked for clinical symptoms and laboratory signs of anaemia 24 h before and after the transfusion of packed red cells. A total of 7998 punctures (average: 4.8 per infant per day) were performed, the mean blood loss due to diagnostic sampling was 50.3 ml/kg per 28 days (range 7–142) for all infants. A high correlation ($r_s = +0.91$) was found between the blood volumes sampled and transfused. In group A, the mean blood loss was 24 ml/kg, and a total of 29 blood transfusions were administered. The most frequent symptoms of anaemia were poor weight gain and apnoeic spells. In group B, the mean blood loss was 60 ml/kg and a total of 97 blood transfusions were administered. In group C, the mean blood loss was 67 ml/kg and a total of 116 blood transfusions were administered. In both groups B and C, poor weight gain, pallor and distended abdomen were the most frequent symptoms of anaemia. Following the blood transfusion, haematocrit rose and blood pressure remained unchanged. The symptoms that responded most favourably to the blood transfusion were: poor weight gain, oxygen requirement, and distended abdomen. The results emphasize the need for miniaturizing laboratory techniques and monitoring blood sampling.

Key words: Anaemia, non-physiological, preterm infant – Diagnostic blood sampling – Blood transfusion

Introduction

Physiological anaemia is common in young infants due to enriched oxygen saturation, increased oxygen unloading capacity (or decreased oxygen affinity) of haemoglobin, decreased erythropoietin production, rapid destruction of HbF cells, and haemodilution by growth. Therefore, "normal", haematocrit decreases markedly during the 1st month of life. In the fetus, erythropoetin is produced primarily in the liver and is less sensitive to hypoxia, which may protect the healthy fetus from hyperviscosity [7]. The erythropoietin response to decreased oxygen availability diminishes in preterm infants as compared to anaemic adult patients [2, 27]. The more immature the infant the lower his level of erythropoietin and the lower the response to anaemia [8]. A possible explanation for the low erythropoietin level could be the slow perinatal shift of erythropoietin production from the liver to the kidneys. In addition, hypovolaemia may occur due to perinatal haemorrhage, inadequate fluid intake, or use of diuretics. Blood loss due to diagnostic sampling has been described as the most common cause of anaemia in hospitalized infants [1, 25] and intensifies "non-physiological" anaemia of the premature infant [31].

The purpose of this study was to measure the amount of blood loss due to diagnostic sampling and to look for symptoms indicating anaemia in small preterm infants.

Patients and methods

Sixty very low birth weight infants who survived the neonatal period were studied within 24 h before and after transfusion of packed red cells. Birth weights ranged from 560–1490 g, gestational age from 25–36 weeks. The study was limited to the first 28 days of life.

Infants were classified according to Hjalmarson [12] into three groups.

A. Infants with spontaneous breathing ($n = 19$), who never required ventilator support. In this group, birth weights ranged from 1050–1490 g and gestational age from 30–32 weeks.

B. Infants with minor respiratory problems ($n = 20$), who required ventilator support after birth, but did not suffer from respiratory distress syndrome (RDS). Diagnoses in this group were asphyxia, wet lung, infection, and pneumothorax. The mean duration of ventilation was 19.2–12.4 (4-42) days. Birth weights ranged from 560–1370 g, gestational age from 26–31 weeks.

C. Infants with RDS = surfactant deficiency ($n = 21$) as diagnosed from the chest X-ray according to Giedion et al. [11]. All infants were ventilated, the mean duration of ventilation being 28.6–20.6 days (6-86 days). Birth weights ranged from 680–1450 g, gestational age from 25–31 weeks.

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Abbreviations: RDS = respiratory distress syndrome; Hb = haemoglobin

Table 1. Blood volume required for frequently ordered laboratory tests. Sampling frequency in the study groups within 28days (Median and range)

Test	Method	µl	Spontaneously breathing (group A)	Minor respiratory problems (group B)	Respiratory distress syndrome (group C)
Blood gases	Radiometer	80	12 (2–40)	106 (22–258)	201 (17–298)
Complete blood count with differential	Sysmex-Counter	500	12 (6–18)	18 (13–28)	19 (12–29)
C-reactive protein	Nephelometry	200	3 (0–7)	3 (0–7)	3 (0–10)
Coagulation	Schnittger	1000	0 (0–1)	0 (0–2)	1 (0–4)
Glucose	Hexokinase	20	19 (6–52)	41 (28–87)	62 (26–68)
Na, K, Ca,	Flame-Photometry	200	10 (7–17)	17 (11–29)	19 (13–36)
Mg	Xylidylblue	50	1 (0–11)	2 (0–7)	2 (0–6)
Total protein	Biuret	200	10 (6–17)	15 (9–23)	18 (9–27)
Bilirubin total	Bilimeter	80	9 (1–28)	14 (3–30)	14 (3–24)
Bilirubin free + conjugated	Jendrassik	600	2 (0–8)	2 (1–12)	3 (2–7)
Urea, Creatinine	Urease, Jaffé	80	2 (0–6)	3 (0–7)	6 (1–16)

Patient management

At birth (most infants were born by Caesarean section), the cord was clamped immediately in an attempt to accelerate resuscitation and to prevent heat loss. Fluid administration was 70 ml/kg on the 1st day of life and was increased within 2 weeks to a maximum of 150 ml/kg. Mechanical ventilation was performed with a time-cycled, pressure-limited Stephan ventilator (Heyer, Bad Ems, FRG). Blood loss due to diagnostic sampling was estimated using graduated Sarsted Z-1 tubes (Sarsted, Nümbrecht, FRG). Transfusions of packed red cells were given when clinical symptoms of anaemia were present and venous haematocrit was below 40%. The transfusion volume usually was 10 ml/kg and was administered in two to three portions within 10 h. This volume may be suboptimal in terms of correcting anaemia. However, as the risk of patent ductus arteriosus increases with large volume administration, we prefer to administer smaller transfusions more frequently and aim to find a walking donor (preferably a parent of the infant). The cumulated amounts of blood given and sampled within the first 28 days of life were divided by birth weight and expressed in ml/kg. The amounts of blood required for laboratory testing are indicated in Table 1.

Clinical symptoms

Within 24 h before and after blood transfusion, the following symptoms were recorded:

1. Weight gain ($\geq$ 10 g increase as compared to the previous day).

2. Oxygen requirement, need for artificial ventilation, or presence of apnoeic spells lasting longer than 20 s during spontaneous breathing.

3. Skin colour (as documented in nurse's notes).

4. Gastric retention ($\geq$ 25% of gavage feeding left in stomach at subsequent feeding).

5. Distended abdomen (intestinal loops visible or abdominal wall above the chest wall level [3, 28].

6. Constipation (no stools within 24 h or glycerol enema administered).

The following signs were recorded within 6 h before and after transfusion:

1. Heart rate (ECG-monitor)

2. Blood pressure (Dinamap neonatal)

3. Venous haematocrit (Centrifuge, 26)

4. FiO_2 (during both spontaneous breathing and artificial ventilation).

Chest X-ray's were taken when clinically indicated. For 100 transfusion events, chest X-ray's were taken within 24 h before and after transfusion and were evaluated for radiographic heart size [5, 6] without knowledge of the transfusion history. In these cases, cardiothoracic ratios were measured according to Edwards et al. [10]. Infants with grade 4 RDS (opaque lungs), cardiac malformation, persistent ductus arteriosus, or treatment with diuretics were excluded from calculation of the cardiothoracic ratio.

Statistical evaluation

In the three patient groups, differences in symptoms before and after transfusion were studied with the χ^2 test or with Fisher's exact test, respectively. Differences in signs of anaemia were studied with the Wilcoxon signed rank test. Cumulated blood loss during the first 28 days of life was compared to cumulated transfusion volume with the Spearman rank correlation.

Results

A total of 7998 blood samples was taken from the 60 infants studied within the first 28 days of life, an average of 4.8 punctures per infant per day. Table 2 specifies the sampling events according to study group, age, and site of puncture. The mean blood loss due to diagnostic sampling was 50.3 ml/

Table 2. Number of blood-samplings in the three groups studied (Total, Median, Range)

Time	Days 1–7			Days 8–28		
Group no. of infants	A 19	B 20	C 21	A 19	B 20	C 21
a) *Heelstick*						
Total	430	1035	1436	256	1231	2047
M (range)	23 (7–47)	51 (20–76)	81 (24–113)	18 (2–33)	36 (8–175)	109 (13–200)
b) *Venous*						
Total	154	169	215	121	206	254
M (range)	7 (3–15)	8 (4–15)	9 (6–15)	5 (2–14)	11.5 (2–19)	11 (2–18)
c) *Arterial*						
Total	24	76	156	8	56	124
M (range)	1 (0–4)	3 (1–10)	5 (1–21)	0 (0–2)	1.5 (0–10)	5 (0–14)

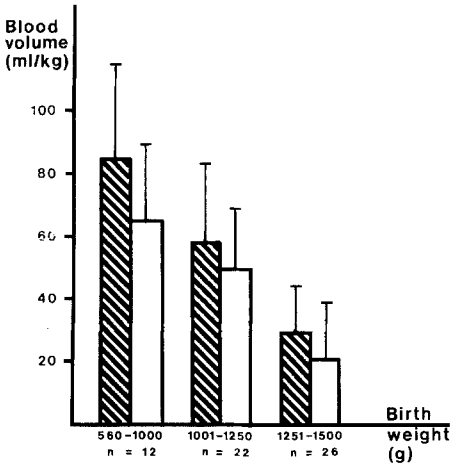

Fig. 1. Cumulated blood volumes sampled *(striped columns)* and transfused *(white columns)* within 28 days versus birth weight classified independently of respiratory failure. Mean and standard deviation

kg during the first 4 weeks of life. This value, as well as the need for transfusion, varied markedly according to birth weight and severity of the disease. Figure 1 shows cumulated diagnostic blood loss and volume transfused for the 60 infants studied, classified by birth weight without regard to respiratory failure.

Table 3 shows, that rather than birth weight, the severity of the disease is more likely to determine the need for repeated blood sampling. Despite lower birth weight, group B infants, mainly small for gestational age with minor respiratory problems, suffered less diagnostic blood loss than those in group C, who were mainly appropriate for gestational age infants with RDS.

Figure 2 shows a high correlation between blood volumes sampled and transfused, and illustrates that in extreme cases blood sampled for laboratory tests exceeded the infant's total blood volume. Symptoms and signs of the infants who never required ventilator support are shown in Table 4. The most frequent symptoms of anaemia recorded in this group were poor weight gain and apnoeic spells. Poor weight gain disappeared frequently after transfusion. Preterm infants with minor respiratory problems are documented in Table 5. In this group, the most frequent symptoms of anaemia were distended abdomen, pallor, and poor weight gain. Low haematocrit and pallor were the only symptoms that significantly improved after transfusion. A slight but significant increase in heart size was observed after transfusion. In RDS (Table 6), the most frequent symptoms of anaemia were pallor, poor weight gain, and distended abdomen. In this group, haematocrit increased and the heart rate and need for oxygen decreased after transfusion. Signs of constipation also appeared less frequently. The 60 infants studied received a mean of 4.0 (range 0–10) blood transfusions during their first 28 days of life. Most of the low birth weight infants not given a transfusion were relatively mature, small for gestational age, not ventilated and left the intensive care unit within a few days. Infants with multiple transfusions were immature, appropriate

Table 3. Birth weight, gestational age, hospital days, cumulated blood volume sampled, number of transfusions and cumulated blood volume transfused within 28 days in three groups of very low birth weight infants (mean ± SD)

Group	Spontaneously breathing (group A) $n = 19$	Minor respiratory problems (group B) $n = 20$	Respiratory distress syndrome (group C) $n = 21$
Birth weight (g)	1343 ± 90	1009 ± 226	1142 ± 185
Gestational age (weeks)	32.5 ± 2.8	29.9 ± 2.7	29.7 ± 1.8
Hospital days	55.7 ± 14.8	91.2 ± 51.5	89.7 ± 31.7
Blood volume sampled (ml/kg per 28 days)	23.8 ± 13.7	59.4 ± 7.7	66.7 ± 27.7
n transfusions	29	97	116
Blood volume transfused (ml/kg per 28 days)	20.5 ± 15.7	52.5 ± 7.4	53.1 ± 20.9

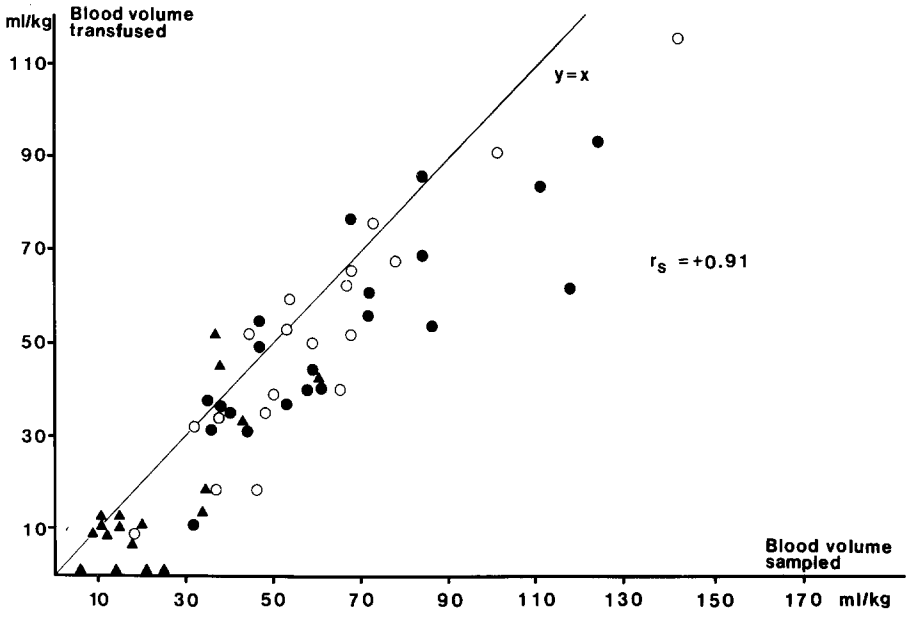

Fig. 2. Correlation of cumulated blood volumes sampled and transfused within 28 days in 60 very low birth weight infants. *Triangles:* spontaneously breathing (group A, $n = 19$). *Open circles:* minor respiratory problems (group B, $n = 20$). *Closed circles:* respiratory distress syndrome (group C, $n = 21$)

Table 4. Signs (Wicoxon signed rank rest) and incidence of recorded symptoms (Fisher's exact test) of anaemia in 19 spontaneously breathing very low birth weight infants (group A) before and after transfusion ($n = 29$, mean ± SD)

Signs and symptoms of anaemia	Before transfusion		After transfusion		*P*
Heart rate	148.5 ± 16.9		145 ± 15.0		n.s.
Blood pressure (systolic)	66.0 ± 12.4		69.5 ± 11.6		n.s.
Haematocrit (venous)	39.7 ± 5.8		45.7 ± 3.4		0.01
FiO_2	21.7 ± 2.4		22.1 ± 5.1		n.s.
Cardiothoracic index ($n = 9$)	46.7 ± 4.1		47.3 ± 5.2		n.s.
	yes	no	yes	no	
Distended abdomen	7	15	5	17	n.s.
Apnoeic spells	11	8	6	13	n.s.
Pallor	6	17	2	21	n.s.
Constipation	4	19	3	20	n.s.
Gastric retention	9	12	10	11	n.s.
Poor weight gain	19	8	5	22	0.01
Any symptoms of anaemia	22	0	15	7	0.01

Table 5. Signs (Wicoxon signed rank test) and incidence of recorded symptoms (χ^2 test) of anaemia in 20 infants with minor respiratory problems (group B) before and after transfusion ($n = 97$, mean ± SD)

Signs and symptoms of anaemia	Before transfusion		After transfusion		*P*
Heart rate	152.4 ± 14.5		148.5 ± 14.3		n.s.
Blood pressure (systolic)	71.7 ± 15.3		71.8 ± 14.8		n.s.
Haematocrit (venous)	38.7 ± 4.5		44.4 ± 4.9		0.01
FiO_2	33.2 ± 17.9		31.7 ± 14.6		n.s.
Cardiothoracic index ($n = 45$)	47.1 ± 4.8		48.5 ± 4.5		0.05
	yes	no	yes	no	
Distended abdomen	50	43	42	51	n.s.
Apnoeic spells after weaning from ventilator ($n = 34$)	15	9	13	11	n.s.
Pallor	48	45	21	72	0.05
Constipation	19	78	15	82	n.s.
Gastric retention	35	58	28	65	n.s.
Poor weight gain	48	46	45	49	n.s.
Any symptoms of anaemia	91	4	61	34	0.01

for gestational age, required prolonged artificial ventilation and suffered from both perinatal haemorrhage and RDS.

Discussion

The aim of our study was to measure the amount of blood drawn for laboratory studies and to re-assess the impact of diagnostic blood sampling in very low birth weight infants receiving various degrees of intensive care.

Non-physiological anaemia

During intensive care of adults, a mean daily volume of 41 ml blood was drawn in patients with arterial lines, even up to 74 ml, and there was a mean total diagnostic blood loss of 944 ml in 13 days [24]. Infants requiring intensive care for several weeks need frequent monitoring of blood gases, blood chemistries, and haematologic status [21, 31, 34]. We were surprised, however, by the large number of punctures to which our infants were subjected. Diagnostic sampling is a major source of blood loss in very low birth weight infants in whom 10 ml blood may represent more than 10% of the total blood volume. According to Blanchette and Zipurski [1], blood sampling is the most common cause of anaemia seen in premature infants. In a 2-day period 10%–15% of the infant's blood volume can be removed [21]. In our hospital, measurement of blood gases requires the largest number of samples. Infants on

Table 6. Signs (Wicoxon signed rank rest) and incidence of recorded symptoms (χ^2 test) of anaemia in 21 very low birth weight infants with respiratory distress syndrome (group C) before and after transfusion ($n = 116$, mean ± SD)

Signs and symptoms of anaemia	Before transfusion		After transfusion		P
Heart rate	151.5 ± 17.3		147.3 ± 14.2		0.05
Blood pressure (systolic)	70.6 ± 18.6		71.9 ± 13.4		n.s.
Haematocrit (venous)	37.6 ± 4.4		43.9 ± 4.3		0.01
FiO_2	33.4 ± 16.3		30.4 ± 13.1		0.01
Cardiothoracic index ($n = 46$)	48.2 ± 5.1		48.6 ± 5.2		n.s.
	yes	no	yes	no	
Distended abdomen	55	59	47	67	n.s.
Apnoeic spells after weaning from ventilator ($n = 24$)	8	16	6	18	n.s.
Pallor	81	34	54	61	0.05
Constipation	28	86	16	98	0.05
Gastric retention	43	53	35	61	n.s.
Poor weight gain	60	42	49	52	n.s.
Any symptoms of anaemia	111	3	80	34	0.01

ventilators had up to 15 gas tests ordered per day. In addition to the sample sent to the laboratory, up to 100 µl blood may disappear into swabs and towels at each sampling.

Few studies have been published that evaluate the diagnostic blood loss in infants below 1500 g [1, 18, 33]: in these studies, however, diagnoses of the infants' condition, need for artificial ventilation, and the level of intensive care were not indicated. In the study of Nexø et al. [18], 1–13 samples were collected from each infant per day, the average blood loss within 4 weeks was 7–51 ml/kg and 25% of the collected blood volume exceeded the amount necessary for the laboratory. In the study of Blanchette and Zipurski, 46 ml/kg whole blood was sampled during the first 6 weeks of life [1], compared to 50 ml/kg in our infants within 4 weeks. The blood volume required by the laboratory was not significantly smaller than in our hospital, so we assume, that more tests were ordered in our infants. In agreement with our results, Blanchette and Zipurski showed that twice as much blood was collected in clinically ill patients than in "healthy" preterm infants. Yu et al. recorded an average diagnostic blood loss of 38 ml in infants weighing less than 1000 g at birth [34], but did not specify the body weight or sampling period.

Pathophysiological consequences

In anaemia, the level of available oxygen (reserve before cardiac output increases at rest) is diminished [13]. There is a linear correlation between available oxygen per g haemoglobin (Hb), gestational age, and postnatal age of preterm infants [31]. It has been emphasized by Scholander [23] that in hypovolaemia and hypoxia the body responds with a redistribution of blood flow: The "diving reflex" augments the blood flow to organs with a high oxygen need and diminishes the blood flow to others. Newborn infants respond to hypovolaemia with a drop in peripheral blood flow, an increase in total peripheral resistance, and a slight reduction of systolic blood pressure [16]. In hypovolaemia the cerebral blood flow remains unchanged, the blood flow to gut and carcass decreases markedly, and the blood flow to kidneys and skin varies according to cardiac output [30]. In hypoxaemic newborn piglets, Szabo et al. [28] found decreased blood flow to the stomach, jejunal and ileal mucosa and submucosa, and a delayed gastric emptying. Gastric retention was present in more than 40% of our infants with anaemia. Selective mesenterial hypoperfusion contributes to necrotizing enterocolitis [22, 29], a disorder to which very low birth weight infants are especially prone.

Symptoms and signs of anaemia

The total blood volume, which is difficult to measure in the neonate [19], may vary from 70–100 ml/kg according to placental transfusion and postnatal adaptation [15]. In our study, the haematocrit value increased significantly after transfusion in all three groups. In our smallest infants with RDS, symptoms and signs of tissue hypoxia and hypoperfusion were most obvious: In this group, the heart rate, need for oxygen and frequency of constipation decreased after transfusion. In group A a distended abdomen and in group C constipation were symptoms of anaemia, which have been described as milds forms of mesenterial vascular insufficiency by Corday et al. [4]. Gastric residuals were not significantly decreased after transfusion.

Transfusion

Unanimous guidelines for blood transfusion in premature infants are not availalbe [9]. The ultimate criterion establishing the need for transfusion is the evidence of impaired tissue oxygenation. Robinson et al. [20] recommended transfusions for hypotension, metabolic acidosis, and for the replacement of diagnostic blood loss exceeding 10% of the estimated blood volume. Within the 1st week of life, Lubin recommended transfusion when the haematocrit was below 40% in infants with respiratory distress and with the haematocrit below 30% in infants without respiratory distress [17]. Yu et al. transfused when the haematocrit was below 40% or the systolic blood pressure was below 40 mm Hg [34]. Erythropoietin radioimmuno-assay may become available to evaluate the need for transfusion in preterm infants when assay-techniques are improved. Low baseline values of erythropoietin and a decrease in responsiveness must be taken into account [8]. The fact that low birth weight infants usually receive multiple transfusions within the first few weeks of life [27], should lead us to consider the risks when repeated diagnostic samplings are ordered. Foremost is the possibility of transmission of viral infection (cytomegaly, hepatitis B, HIV), described in up to 14% of transfusions [21]. Yaeger et al. [32] have described ten infants with transfusion-acquired cytomegaly, two of them with a lethal course. Rarer complications are graft-versus host reaction, volume overload (persisting ductus arteriosus), antigenic sensitization, haemolytic reactions, and metabolic disturbancies (hyperglycaemia, hyperkalaemia). Replacement of a large proportion of the blood by transfusion leads to a right shift of the oxygen dissociation curve. This enhances oxygen delivery to the tissues and increases the risk of retrolental fibroplasia. Following placental transfusion, the transverse diameter of the heart is larger, especially in asphyxiated infants, whereas

blood pressure is only slightly affected. We found no significant increase in blood pressure following transfusion. Blood transfusion leads to a rise in mean arterial pressure only if it was less than 35 mm Hg before transfusion [20]. Stockman et al. showed that infants who failed to thrive responded positively to transfusion [26].

Conclusions

Everyone who is involved in ordering or collecting blood from preterm infants should be aware of the fact that sampling is a painful and risky procedure, a fact that needs stressing even more as it is an everyday practice in the intensive care unit: in addition to the immediate risks of cutaneous haematomas, necroses, calcifications, chondritis, osteomyelitis, and sudden increase in blood pressure due to pain, blood sampling is a major cause of anaemia in low birth weight infants. Yeh et al. [33] recently have demonstrated a significant increase in oxygen consumption of preterm infants during manipulations. We strongly support the demand of Nexø et al. that orders for blood testing should be restricted to the minimum required for proper clinical management of the preterm infant [18]. Physicians and nurses who draw blood samples must realize the minimum amount required by their laboratory. All efforts should be made to miniaturize laboratory procedures towards ultra-micro-assays. The blood volumes sampled should be measured and recorded in the infant's chart [1, 34]. Premature infants going through intensive care should be monitored closely for symptoms and signs of anaemia such as apnoeic spells, feeding difficulties, and failure to thrive.

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