

STAT testing in the neonate

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Babies are not small adults! The potential for abnormal adaptation to life outside of the womb, changes in physiology, and a myriad of possible life-threatening clinical conditions requires an understanding of the laboratory tests needed to support these infants.

To effectively handle the unique needs of these patients, laboratories must be able to offer rapid turnaround times (TAT) for critical analytes, be knowledgeable about correct collection techniques and sample handling requirements, perform testing on instrumentation with the appropriate analytical ranges for infants, and assist in the interpretation of results.

Introduction

Birth and adjustment to life outside of the mother create rapid physiologic changes. These may require aggressive monitoring, often with the support of laboratory tests. In addition, there are a number of abnormal conditions affecting the newborn that require laboratory support.

The consequences of NOT providing adequate monitoring may result in morbidity or mortality that can manifest itself immediately or later in life. This review provides an examination of and rationale for the common clinical laboratory tests performed on neonates.

By gestational age:	Neonate	37-42 weeks gestation
	Preterm	< 37 weeks gestation
	Extremely preterm	< 30 weeks gestation
By birth weight:	Low birth weight	< 2.5 kg
	Very low birth weight	< 1.5 kg
	Extremely low birth weight	< 1 kg
Other classifications:	Small for gestational age	(SGA)
	Appropriate for gestational age	(AGA)
	Large for gestational age	(LGA)

TABLE I: Commonly used terms for the classification of neonates

What is a neonate?

While the term “infant” applies to a child less than one year of age [1], “neonate” describes the period immediately after birth to 28 days old.

Table I [2] describes the commonly used terms to describe a neonate, generally based on gestational age and birth weight [3]. Neonates born before 37 weeks of age are classified as preterm.

Preterm birth is the second leading cause of neonatal mortality in the United States [4]. From 1989 through 1996, the overall rate of preterm births per 1,000 live-born infants increased 4 % and the rate of multiple births, associated with preterm birth, increased 19 %. Mortality rates increase significantly for infants born before 24 weeks’ gestation.

Though there is no defined lower weight limit for survival, very few babies born less than 500 g survive [3].

Analyte	Adult Range	Full-term Newborn-Range
Albumin	3.7-5.6 mg/dL	2.6-3.6 mg/dL
Total protein	6.3-8.6 mg/dL	3.4-7.0 mg/dL
Alkaline phosphatase	50-175 IU/L	50-400 IU/L
Ionized calcium	4.8-5.3 mg/dL	4.8-6.0 mg/dL
Uric acid	1.8-5.0 mg/dL	3.0-8.6 mg/dL
Thyroxine	4.9-10.0 µg/dL	5.9-21.5 µg/dL
Total bilirubin	< 1 mg/dL	< 12 mg/dL
CKMB	< 2.0 %	1.5-8.0 %
Phosphorus	2.8-4.6 mg/dL	4.6-8.0 mg/dL
Ammonia	< 35 µmol/L	< 50 µmol/L

TABLE II: Examples of differences in reference intervals between adults and neonates.

Note: Reference intervals will vary depending on instrument and method used.

Physiological differences of the neonate

At birth, most biochemical parameters of the neonate are similar to those of the mother.

Examples of differences are listed on **Table II**. Calcium, phosphorus, and alkaline phosphatase are higher due to placental effects. Plasma proteins do not cross the placenta and reflect intrauterine nutrition.

A full-term infant may have a water content as much as 20 % higher than an older infant. The water content of a preterm baby may be higher if calculated as a proportion of total body weight, due to an increase in extracellular fluid [5].

Fat content is a function of gestational age. For example, a baby born at 28 weeks’ gestation may have a fat content of 3.5 % while the fat content of a full-term infant is about 15 %.

Liver function is affected at birth due to hepatic immaturity, resulting in a slower rate of metabolism and

excretion of substances. Physiological jaundice is a result of altered liver function, and occurs in about one third of all newborn babies [5, 6].

Abnormal liver function can also be caused by underlying disease, such as neonatal hepatitis, or as a result of a structural abnormality such as biliary atresia.

Prior to birth, the fetal lungs contain a clear fluid containing phospholipid, which is expelled into the amniotic fluid when the fetus is apneic. The amniotic fluid can be used to assess fetal lung maturity by measuring the ratio of lecithin to sphingomyelin; lecithin production increases towards the end of gestation [5].

Following birth, lung liquid production stops. Pulmonary gas exchange must be established within minutes. In addition, the fetal cardiovascular system changes from two circulations in parallel, involving the placenta, to two circulations in series.

There may be difficulties in pulmonary and/or cardiovascular conversion, leading to serious cardiorespiratory dysfunction in the neonate. Aggressive assessment of oxygenation (pO_2), alveolar ventilation (pCO_2), and acid-base status (pH, HCO_3^-) is essential to evaluate cardiorespiratory activity and monitor therapy [7].

There are a number of inherited metabolic disorders which present clinically in the neonatal period. The metabolic disorders most likely to present are those due to defects in small-molecule metabolism (e.g. amino acids, organic acids, carbohydrates, and urea cycle products) [8].

The severity of the conditions mentioned above requires close monitoring of the infant using a number of laboratory and physiologic tests. Delivery of this care is most often and most effectively done in the neonatal intensive care unit (NICU), where specially trained neonatologists, nurses, respiratory therapists, and other pediatric specialists attend the needs of these children.

Phlebotomy considerations

Heel sticks and draws from arterial lines are the most commonly used sites for blood draws. Heel sticks require a high degree of technical expertise to be done properly and without inflicting unnecessary pain or harm to the infant [9].

For line draws (e.g. indwelling catheters), the catheter should be cleared of flush solution or perfusate prior to drawing blood to avoid dilution or contamination of the specimen. Frequent blood draws for laboratory testing create the risk of iatrogenic anemia. It has been estimated that 64 % of infants < 1500 g receive transfusions for anemia [10] due in part to frequent or excessive blood draws.

With a plasma volume of 4-5 % of body weight, a 1,500 g infant has a total of 70 mL of plasma. Blood transfusion may be required when 10 % or more of a neonate's blood volume is withdrawn in 2-3 days. This amount represents about 80 mL/kg of body weight for a full-term infant, and about 100 mL/kg for a preterm infant.

The volume and number of blood draws have been reduced in recent years due to transcutaneous monitoring and newer equipment [11]. Minimizing the need for blood draws reduces the subsequent need for transfusion as well as the risk associated with transfusion.

Use of a daily log that tracks the blood volume drawn for all critically ill and preterm neonates is recommended. Laboratories should provide clinicians with the minimum sample volumes required for each test or group of tests performed.

Most of the current clinical chemistry analyzers require small sample volumes for testing, with many analytes using less than 10 μ L each of serum or plasma. The hematocrit of an infant can be > 60 %, reducing the volume of serum or plasma in the collection container.

The "dead volume", consisting of the volume of specimen that must be in the instrument's sampling container, is required in addition to the specimen volume

and should also be minimal for neonatal applications.

In addition to the expertise required to draw an appropriate specimen, use of microcontainers and labeling the containers correctly is more labor-intensive than handling larger specimens. Appropriate handling and testing of neonatal specimens require:

1. A laboratory staff specifically trained to handle small specimen sizes.
2. Understanding of the effects from commonly found interferences (e.g. bilirubin, lipemia, hemolysis).
3. a laboratory properly equipped with instrumentation that can handle small sample sizes and provide rapid turnaround times consistent with clinical requirements (**Table III**) [7].

Utilization and ordering patterns have an impact on laboratory services and the patient. Though aggressive monitoring may be required for a particular patient, studies involving NICU test-ordering patterns indicate that less experienced interns order more tests per infant than more experienced residents [12].

Reference intervals

Age-specific reference intervals are critical for the appropriate interpretation of results. These can be very difficult to obtain for individual laboratories. Due to the growing number of preterm neonates, the need becomes greater for age-related gestational and postnatal reference ranges.

Test	Availability		TAT*
Blood gasses (pH, pCO₂, pO₂)	24 hours/day		< 10 min
Sodium	24 hours/day	STAT non-STAT	< 30 min 2 hours
Potassium	24 hours/day	STAT non-STAT	< 30 min 2 hours
Glucose	24 hours/day	STAT non-STAT	< 30 min 2 hours
Calcium	24 hours/day	STAT non-STAT	< 30 min 2 hours
Albumin	Daily		< 8 hours
PT	24 hours/day		< 4 hours
PTT	24 hours/day		< 4 hours
Ammonia	24 hours/day		< 1 hour
ALT	Daily		< 8 hours
Alkaline phosphatase	Daily		< 8 hours
GGTP	Daily		8-12 hours
Total bilirubin	24 hours/day		< 2 hours
Conjugated bilirubin	24 hours/day		< 5 hours
Drug screen**	24 hours/day	Initial confirmatory	< 4 hours < 24 hours
Amino-glycosides (Gentamicin, Tobramycin, Amikacin)	2-4 hours/day		< 2 hours
Vancomycin	24 hours/day		< 2 hours
Theophylline	24 hours/day		< 2 hours
Digoxin	24 hours/day		< 30 min < 2 hours
Phenobarbital	24 hours/day		< 2 hours
Phenytoin	24 hours/day		< 2 hours

TABLE III: Recommended availability and turnaround time (TAT) for assessment/ monitoring of the neonate.

*TAT refers to time interval between specimen collection and results.

** Urine should be collected as soon as possible after birth, or within 1-2 days

Since “normal” ranges cannot be applied to preterm, and since obtaining permission for specimens is increasingly difficult, laboratories are dependent upon published reference ranges [13, 14] and validating these ranges as best as possible.

For proper interpretation of results, clinicians must be aware of circumstances where reference intervals for gestational age are not available or adult reference intervals are used.

Neonatal cardiac and respiratory function

Oxygen delivery to the tissues depends upon the oxygen-carrying capacity and oxygen saturation of hemoglobin, and on cardiac and respiratory function.

Hypoxia is associated with pulmonary hypertension, decreased pulmonary blood flow, acidosis and organ damage [15, 16], and may be caused by low cardiac output, congenital heart disease, lung disease, anemia or hemoglobin variants [7].

Hyperoxia, which may occur with oxygen administration in a preterm neonate, is associated with an increased incidence of retinopathy of prematurity and other forms of oxygen toxicity [17, 18]. The therapeutic goal is adequate delivery of oxygen without undue stress on the organs, such as the lung and retina.

Oxygenation, alveolar ventilation, and acid-base status must be monitored during the neonatal period when cardiac and/or respiratory dysfunctions occur. This can be done both at the bedside and in the laboratory.

Blood gas measurements, often referred to as arterial blood gases (ABG), are necessary in the diagnosis of hypoxia and hyperoxia. Continuous non-invasive monitoring of oxygen saturation of hemoglobin by pulse oximetry is a useful tool for oxygen monitoring in the NICU [16, 19, 20].

Caution should be given to interpreting ABG values in patients with hyperbilirubinemia, anemia, or those receiving hyperalimentation. ABG specimens from

patients with these conditions may not correlate with pulse oximetry.

Pulse oximetry measures oxygen saturation ($sO_2(a)$) and transcutaneous oxygen monitors measure the partial pressure of arterial oxygen ($pO_2(a)$). Though each has limitations, these non-invasive devices monitor trends in oxygenation and are easy to use.

The frequency of validation of quantitative ABG measurement depends on the clinical situation of the infant. $sO_2(a)$ values obtained by pulse oximetry should be validated by direct CO-oximetry from an indwelling arterial catheter.

Blood gas measurements should be performed every six hours for stable infants and more frequently for critically ill infants [21]. Fetal hemoglobin (HbF) is present in newborns for about six months, it has a higher affinity with oxygen and saturates at a lower pO_2 than HbA [22]. Pulse oximetry is less susceptible to this shift than CO-oximetry for monitoring O_2 saturation.

Newer technologies for measuring blood gases include continuous *in vivo* and *ex vivo* monitoring systems [23-25]. *In vivo* monitors for blood gases require placement of a sensor/detector in the patient's radial artery while *ex vivo* monitors draw blood through a catheter, perform measurements externally, and return the blood to the patient. These systems allow for continuous or frequent monitoring without blood loss.

The balance between metabolic carbon dioxide (CO_2) production and ventilatory CO_2 excretion can be estimated by measuring the partial pressure of carbon dioxide (pCO_2) in arterial blood [19].

Management of an increased pCO_2 may involve decreasing CO_2 production (e.g. sedation, reduction of thermal stress) or by increasing ventilation (e.g. increasing ventilator rate or tidal volume, reducing airway resistance, administering surfactant).

Direct pCO_2 can be measured by ABG or by non-invasive monitors using transcutaneous CO_2 ($tc pCO_2$)

or end tidal CO₂ (pCO₂(ET)) monitoring. Though the tcpCO₂ method is preferred for preterm neonates, each device has limitations that require validation by ABG measurements.

<p>Metabolic Acidosis:</p> <ul style="list-style-type: none"> • Insufficient renal acid secretion • Shock • Sepsis • Intraventricular hemorrhage • Diarrhea • Hypoxemia
<p>Respiratory Acidosis:</p> <ul style="list-style-type: none"> • Lung disease • Upper airway obstruction • Central nervous system depression • Neuromuscular disease • Excessive artificial ventilation
<p>Metabolic Alkalosis:</p> <ul style="list-style-type: none"> • Complication of diuretic therapy • Therapeutic bicarbonate infusions
<p>Respiratory Acidosis:</p> <ul style="list-style-type: none"> • Inadequate artificial ventilation

TABLE IV: Clinical conditions associated with disturbances in acid-base status

The assessment of acid-base status is critical in the compromised neonate. The most common causes of metabolic and respiratory acidosis and alkalosis are listed in **Table IV** [32].

Specimens are obtained from arterial puncture, skin puncture (heel or finger) or from an indwelling catheter placed in the aorta via the umbilical artery or a peripheral artery [26]. Blood obtained from indwelling catheters yields the most accurate measurement of pO₂(a); however, there are risks associated with thrombosis and infections.

Indwelling catheters should be flushed and a few drops of blood discarded before collecting the specimen. The

radial artery is the usual site for performing an arterial puncture; however, these are hurtful to the baby and cause crying leading to changes in pO₂(a).

The amount and type of heparin used to anticoagulate the blood must be considered. For example, increased amounts of heparin solution dilute the blood and falsely decrease pCO₂ and bicarbonate.

Electrolytes measured on the same sample as ABG can yield falsely elevated sodium or potassium, if sodium heparin and potassium heparin are used. Dry lithium heparin is recommended to avoid dilution effects [19, 27].

Skin puncture, or capillary blood, is obtained from the heel or, less frequently, the finger. Reliable results come from optimizing techniques for obtaining the specimen, adequate perfusion, avoidance of air bubbles and dilution from anticoagulant [9]. Capillary pO₂ measurements are unreliable in ill infants and not recommended [7].

The volume of specimen required for blood gas measurements varies from 45 µL to 400 µL, depending on the number of analytes being measured (e.g. blood gases, electrolytes, etc.) and the instrument selected.

Although a specimen is considered stable up to 15 minutes for blood gas measurements [19, 28], the preferred protocol is a specimen collected in a plastic syringe, not placed on ice, and analyzed within 10 minutes.

All parameters for ABG (measured and calculated) should be reported, including pO₂, pCO₂, pH, calculated bicarbonate, and calculated base deficit/excess. Effective communication between the laboratory and the NICU is essential for establishing mutually acceptable turnaround times and appropriate age-related reference intervals.

Analyte		Conventional Units	SI Units
Sodium		135-145 meq/L	135-145 mmol/L
Potassium**		3.6-6.7 meq/L	3.6-6.7 mmol/L
Chloride		101-111 meq/L	101-111 mmol/L
Glucose		40-150 mg/dL	2.2-8.3 mmol/L
Total Calcium	Full term	8-11 mg/dL	2.0-2.75 mmol/L
	preterm	7-11 mg/dL	1.75-2.75 mmol/L
Ionized Calcium	< 72 h	4.4-5.6 mg/dL	1.1-1.4 mmol/L
	> 72 h	4.8-6.0 mg/dL	1.2-1.5 mmol/L

TABLE V: Reference intervals for electrolytes*

* Plasma values

** Potassium is 0.2-0.3 mmol/L lower in plasma than in serum in adults due to release of potassium into serum during clotting.

Fluid and electrolytes

Small changes in water and electrolyte intake or loss may produce relatively large changes in total body water and electrolyte content. The preterm infant is especially vulnerable to large water losses through the surface area of the skin and as a result of a higher skin permeability [29, 30].

For example, a loss of extracellular water may lead to a weight loss of 5-10 % in a term infant and 10-20 % in a preterm infant during the first week of life. Routine fluid and electrolyte testing includes sodium, potassium, chloride, calcium (total and ionized), glucose, and creatinine. Laboratory monitoring for these tests may be necessary as often as every 6-12 hours (see **Table III**).

For example, hyperkalemia may develop in extremely preterm neonates following a potassium shift from the intra- to the extracellular space during the first few days of life [31]. Reporting of potassium on visibly hemolyzed specimens should be avoided. It is recommended that whole-blood potassium confirm a serum potassium if > 6.5 mmol/L or if the change from the previous value is > 0.5 mmol/L.

Serum potassium is higher by 0.2-0.3 mmol/L than plasma or whole blood due to the release of potassium from platelets during the clotting process [31]. To minimize hemolysis, the preferred blood sample for

confirming a critical result from skin puncture is one obtained by venipuncture or from an intravascular catheter.

Testing for chloride is required less often than for sodium and potassium, because chloride changes parallel those of sodium. Interpretation of chloride values is dependent upon the infant's environment, age, acid-base status, and fluid and electrolyte intake [32].

Calcium rises in the first hours of life following a parathyroid hormone response, and drops by 24-48 hours. Total calcium underestimates physiologically active calcium (ionized calcium), if the serum albumin and/or pH are low. Therefore, ionized calcium is the preferred measurement when an accurate assessment is needed, particularly in hypocalcemia of the preterm infant [33].

Neonates are at risk of hypoglycemia immediately after birth [34], with the risk increased in preterm neonates whose hepatic glycogen stores are low [35]. Hyperglycemia, particularly in the preterm infant, may occur following glucose administration due to a sluggish insulin response [36].

Frequent monitoring is required in these patients, often performed using point-of-care (POC) glucose monitors. Because of the higher hematocrit levels in neonates in general, and neonates receiving oxygen therapy in

particular, devices and test strips must be evaluated and correlated to laboratory methods for appropriate interpretation of results [37, 38].

In addition, there is a difference of about 11 % between whole-blood POC glucose and serum or plasma values. Although there is no uniform agreement for the cutoff value for hypoglycemia, critical glucose results (generally < 40 mg/dL, 2.2 mmol/L) obtained by POC devices should be confirmed by the laboratory.

Creatinine in the first few days of life reflects maternal function. Interpretation of creatinine results is complicated by rapid changes in extracellular volume and glomerular filtration rate [39]. Changes in creatinine vary with gestational age, and the absence of an expected drop may indicate compromised renal function [40].

Hepatic function and bilirubin

The synthetic and clearance functions of the liver can be assessed by measuring the intracellular constituents. The liver's synthetic capacity may be evaluated by measuring serum albumin and coagulation factors; however, albumin is a less sensitive marker due to its long half-life (19-21 days) and a decrease is not specific for liver disease (e.g. albumin is decreased in protein-losing enteropathies or from inadequate protein-calorie intake) [41, 42].

Monitoring serum albumin weekly is sufficient unless there is an acute change, such as edema or ascites. Serum coagulation factors, except factor VIII, are synthesized in the liver and are sensitive indicators of synthetic liver function. Prothrombin time (PT) and partial thromboplastin time (PTT) have short half-lives and reflect acute liver disease.

Elevated PT and PTT values are not specific since they are dependent upon vitamin K for activation, and conditions affecting vitamin K will result in prolonged PT and PTT results [43]. Specimens should be collected in a tube containing citrate as the anticoagulant, and transported to the laboratory on ice within 30 minutes [44, 45].

Blood drawn from an indwelling catheter containing heparin may alter the PTT. The ratio of blood to citrate may need to be adjusted for hematocrits > 50 %, as commonly seen in neonates, and < 20 %.

Hepatic clearance can be evaluated by measuring ammonia concentrations. The majority of ammonia is removed from venous blood in one pass through the liver, but diminished liver function decreases ammonia clearance by the liver, leading to increased blood ammonia levels. Increased ammonia levels may also be seen in certain metabolic diseases, including defects of the urea cycle and of mitochondrial fatty acid β -oxidation [46].

Specimens for measurement of ammonia must be collected without a tourniquet using heparin as the anticoagulant. The specimen should be immediately placed in an ice-water mixture and transported to the laboratory. Analysis within one hour will minimize the conversion of glutamine to ammonia. Glutamine conversion can increase ammonia concentrations by 0.017 mg/mL/min at 25 °C [41].

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are sensitive indicators of damage to the organs or tissues containing these enzymes [47].

They are not specific for hepatocyte injury, though ALT is more sensitive to hepatocellular injury than AST. Alkaline phosphatase and gamma-glutamyl transpeptidase (GGTP) are indicators of cholestasis, though not very specific [48, 49].

Alkaline phosphatase activity, used in adults to assess obstructive jaundice, is less useful in neonates because osteoblastic bone activity associated with growth produces elevations. Age-specific reference intervals are critical to interpretation of alkaline phosphatase.

GGTP is a sensitive indicator of hepatic injury and cholestasis [49]. Preterm infants may have higher GGTP activities than term infants during the first few days of life. Infants < 6 months old may have serum GGTP

activities 5-8 times the upper limit of normal for adults [14, 50]. GGTP can help with the interpretation of elevated serum alkaline phosphatase in distinguishing liver damage from other causes.

Hyper-bilirubinemia

Jaundice is the visual product of bilirubin deposits in the skin and mucosal membranes. Total and direct bilirubin measurements in serum are central to the classification of liver disorders into pre-hepatic, hepatocellular, and biliary tract conditions [5].

The immature liver of the infant is faced with an increased load of fetal hemoglobin as it tries to convert fetal to adult hemoglobin. Increased levels of unbound serum bilirubin cross the blood-brain barrier in a neonate, increasing the risk of bilirubin encephalopathy.

If not treated, increased bilirubin can lead to neurotoxicity, convulsions, and perhaps death [51]. Conditions that expose a neonate to bilirubin toxicity include:

1. The bilirubin binding sites on albumin are saturated.
2. The infant is hypoalbuminemic.
3. Concurrent acidosis.
4. Treatment with drugs that displace bilirubin from albumin.

Sepsis, hypoglycemia, and hyperosmolarity can further compromise the blood-brain barrier, increasing the risk of bilirubin encephalopathy [52], which usually occurs at concentrations >25 mg/dL.

Jaundice is seen in about 60 % of term and 80 % of preterm neonates during the first week of life, and becomes apparent at serum bilirubin concentrations of >5 mg/dL (85 μ mol/L) [53]. Physiologic jaundice is defined as an elevated unconjugated bilirubin of >13 mg/dL (>212 μ mol/L) in the first week of life.

Unconjugated hyperbilirubinemia peaks by day 3 of life at 5-8 mg/dL (85-137 μ mol/L) for term neonates and at 8-15 mg/dL (137-256 μ mol/L) by days 5-7 for

preterm neonates. The causes of physiologic jaundice are bilirubin overload, increased production (neonates produce 8-10 mg bilirubin/kg body weight while adults produce 3.6 mg bilirubin/kg body weight), an increased ratio of RBCs to body weight as compared to adults, and a shorter RBC lifespan.

There is also a decrease in the clearance of bilirubin. The neonate's hepatic conjugation system does not reach maturity until 6-14 weeks of life [54]. Non-physiologic jaundice should be considered when the serum bilirubin concentration is greater than expected (e.g. serum unconjugated bilirubin rises >5 mg/dL/day, clinical jaundice present after one week of life for a term neonate and after two weeks of life for a preterm neonate).

Pathologic hyperbilirubinemia may be classified by whether the primary increase in bilirubin is unconjugated or conjugated [55]. Jaundice should be monitored with total serum bilirubin if the conjugated bilirubin fraction is not elevated.

The mainstay of treatment for elevated levels of unconjugated bilirubin is phototherapy, which converts unconjugated bilirubin to polar fractions that can be excreted in bile. Phototherapy is stopped once total serum bilirubin concentrations fall below 14 mg/dL (239 μ mol/L). If phototherapy is not successful, an exchange transfusion may be required to lower bilirubin levels. Laboratory measurements of total bilirubin are therefore critical in deciding how and when to treat neonatal jaundice.

Bilirubinometers have been used to measure total bilirubin; however, they require larger sample sizes (about 50 μ L) than newer methods on automated analyzers [56]. Non-invasive devices (see below) have been recently introduced for measuring total bilirubin.

Measurement of bilirubin is susceptible to interferences from hemolysis (particularly from heel-stick specimens), lipemia, and exposure to sunlight or ultraviolet light. Steps should be taken to minimize these interferences.

Therapeutic drug monitoring

It has been estimated that during hospitalization, an average number of drugs given to preterm infants <1,000 grams is 15-20 [57]. Neonates have significantly different pharmacokinetic parameters than adults due to their small size and the immaturity of organs that metabolize drugs.

Among these differences are a slower clearance as a result of immature hepatic and renal function, slower biotransformation, and decreased protein binding of the drug. Close monitoring of therapeutic drugs is required to avoid toxicity in these infants.

Smaller size and body weight require slower infusion rates for drugs. Correct timing of specimen collection for drug levels must take into account differences in drug delivery rates [58, 59]. Interpretation of drug levels can vary depending on the method used for analysis [60].

Clinicians and laboratory staff should work together to develop therapeutic ranges, TATs, STAT menu, peak and trough drug parameters, and critical values.

Intrauterine drug exposure

Exposure to drug abuse during fetal life may present with adverse effects following birth. Prompt diagnosis of intrauterine drug exposure (IUDE) will aid in the therapy and management of these infants [61, 62].

Although screening all infants for IUDE is not current practice in the US, protocols for ordering drug screens, threshold concentrations, and confirmation testing should be developed by the laboratory and the neonatologists.

Medical-legal implications of newborn drug testing require that presumptive positive tests be confirmed using a different methodology [63]. The difficulty in obtaining a suitable, timely urine sample from a newborn is challenging, though necessary for reliable results [64].

At least 5 mL of urine should be collected. This volume allows for initial testing, confirmatory testing, and a sufficient amount to retain as an aliquot should there be a discrepancy. For a term neonate, an expected IUDE should be positive for 1-2 days following birth and up to a week in preterm neonates.

Point-of-care testing

Point-of-care testing (POCT) is defined as any laboratory testing performed outside of the clinical laboratory. Most POCT devices require small specimen volumes and provide rapid TAT, making them well-suited to the needs of the ill neonate.

Devices measuring glucose, electrolytes, and blood gases perform these measurements on whole blood, limiting the amount of blood needed and reducing the potential for iatrogenic anemia.

Steps required to send a specimen to the laboratory are eliminated (labeling microtubes, transporting specimen to laboratory) and steps required to process and produce a result reduced. Murthy *et al* [65] evaluated POC testing for whole-blood electrolytes and blood gases on patients in the pediatric and neonatal intensive care units. Testing was performed by nursing staff.

The authors found comparable results to their reference methods (except for pO_2) and observed improvement in TAT, but advised that test utilization and costs should be carefully controlled.

Specimen collection, specimen matrix, interferences (hematocrit, lipemia, bilirubin), and reference intervals should all be evaluated and compared to standard laboratory procedures prior to introducing POCT into the NICU or any other setting.

In addition to POC devices requiring blood specimens, devices are being developed using non-invasive and minimally invasive technologies. The recent introduction of non-invasive bilirubin and glucose devices [23] provide NICUs and pediatricians with the ability to perform these analyses without the need to draw blood.

These and similar devices have the potential for providing fast results and reduce the need for and risks associated with blood transfusions.

Conclusion

Laboratories performing testing on neonates face many challenges. These include the need to respond quickly to test requests, specific training of personnel involved in testing, and an understanding of the unique requirements for appropriate testing in this patient population.

Quality results can be provided, and must be provided, for these patients. The laboratory serves as an ideal resource in providing both quality results and interpretive support to clinicians as they provide optimal care for their patient.

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