SEVENTH EDITION

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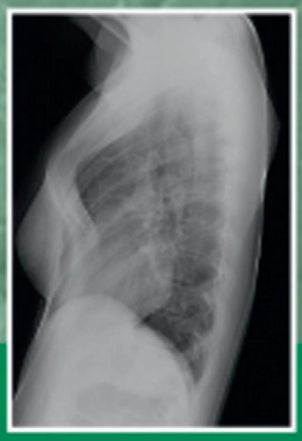

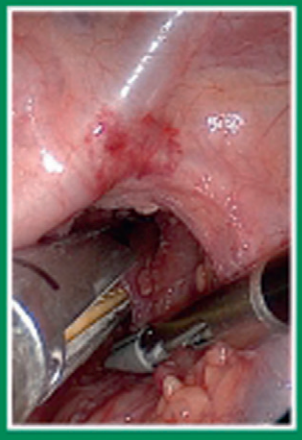

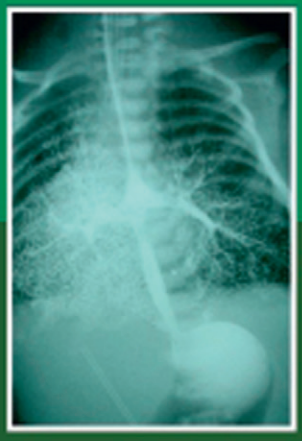

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Holcomb and Ashcraft's Pediatric Surgery

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Holcomb and Ashcraft's Pediatric Surgery

SEVENTH EDITION

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Preface

Welcome to the Seventh Edition of this textbook, which was originally conceived and developed by Drs. Tom Holder and Keith Ashcraft. The first edition was published in 1980. We continue to hold dearly several tenets of this book: readability, an international perspective, an emphasis on general pediatric surgery and urology, and portability. In the Preface of the Second Edition, Drs. Holder and Ashcraft wrote, "Our intent is to provide a book that has a clear explanation of a subject done in a readable style." Our readers live all over the world, and, for this reason, we have many authors who practice outside the United States. Also, urology is a significant part of an international pediatric surgeon's practice, and we have continued to have a relatively large portion of the book devoted to pediatric urology. Finally, for ease of access to the book, it remains a single volume book and is available online.

In this edition, we have a number of new authors and many returning authors. There has been significant updating of the text and illustrations. All the illustrations are in color. Also, a large number of figures are new to this edition.

Finally, there are over 50 videos that accompany this book and are designed to help the reader better understand many of the operative techniques described in the chapters. These videos are accessible via our Expert Consult website (expertconsult.com). The code in the front of this book allows access to the online version of the book and the videos.

We are very pleased to acknowledge Mrs. Barbara Juarez, Mrs. Linda Jankowski, and Mrs. Jeannette Whitney, who have been instrumental in the behind-the-scenes production of the last several editions of this book. All three will be retiring soon, and we are truly indebted to their tireless efforts. Their many contributions to our hospital and the editors will be dearly missed in the future. This book is dedicated to these three wonderful colleagues.

Again, we are pleased to offer this book for your education and, hopefully, enjoyment. We look forward to interacting with many of you over the next several years.

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This Seventh Edition of our book is enthusiastically dedicated to three wonderful Administrative Assistants: Mrs. Linda Jankowski, Mrs. Jeannette Whitney, and Mrs. Barbara Juarez. All three have been associated with our group for several decades and have been invaluable in the production of the last four editions of the book.

The Editors

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SECTION I

General

1 Physiology of the Newborn

MARIYA E. SKUBE, BRADLEY J. SEGURA, and DANIEL A. SALTZMAN

Of all pediatric patients, the neonate possesses the most distinctive and rapidly changing physiologic characteristics. These changes are necessary because the newborn must adapt from placental support to the extrauterine environment. There is also early organ adaptation and the physiologic demands of rapid growth and development. This chapter will emphasize the dynamic physiologic alterations of the neonate.

Newborns are classified based on gestational age, weight, head circumference, and length. Preterm infants are those born before 37 weeks of gestation. Term infants are those born between 37 and 42 weeks of gestation, whereas post-term infants have a gestational age that exceeds 42 weeks. With advances in neonatal intensive care, infants born as early as 21 weeks of gestation have survived, and the medical and ethical guidelines regarding the care of these extremely premature neonates continue to evolve.[1] Babies whose weight is below the 10th percentile for age are considered small-for-gestational-age (SGA). Those at or above the 90th percentile are large-for-gestational-age (LGA). Babies whose weight falls between these extremes are appropriate-for-gestational-age (AGA). Further subclassified, premature infants are characterized as moderately low birth weight if they weigh between 1501 and 2500 g, very low birth weight between 1001 and 1500 g, and extremely low birth weight if less than 1000 g.

SGA newborns are thought to suffer intrauterine growth retardation (IUGR) as a result of placental, maternal, or fetal abnormalities. Conditions associated with IUGR are shown in Fig. 1.1.[2] SGA infants have a body weight below what is appropriate for their age, yet their body length and head circumference are age appropriate. To classify an infant as SGA, the gestational age must be estimated by the physical findings summarized in Table 1.1.

Although SGA infants may weigh the same as premature infants, they have different physiologic characteristics. Due to intrauterine malnutrition, body fat levels are frequently below 1% of the total body weight. This lack of body fat increases the risk of hypothermia in SGA infants. Hypoglycemia is the most common metabolic problem for neonates and develops earlier in SGA infants due to higher metabolic activity and reduced glycogen stores. The red blood cell (RBC) volume and the total blood volume are much higher in the SGA infant compared with the preterm AGA or the non-SGA full-term infant. This rise in RBC volume frequently leads to polycythemia, with an associated rise in blood viscosity. Due to an adequate length of gestation, the SGA infant has pulmonary function approaching that of the AGA or a full-term infant.

Infants born before 37 weeks of gestation, regardless of birth weight, are considered premature. The physical exam of the premature infant reveals many abnormalities. Special problems with the preterm infant include the following:

1. Weak suck reflex
2. Inadequate gastrointestinal absorption
3. Hyaline membrane disease (HMD)
4. Intraventricular hemorrhage
5. Hypothermia
6. Patent ductus arteriosus
7. Apnea
8. Hyperbilirubinemia
9. Necrotizing enterocolitis (NEC)

Specific Physiologic Problems of the Newborn

GLUCOSE METABOLISM

The fetus maintains a blood glucose value of 70–80% of maternal levels by facilitated diffusion across the placenta. There is a build-up of glycogen stores in the liver, skeleton, and cardiac muscles during the later stages of fetal development, but little gluconeogenesis. The newborn must depend on glycolysis until exogenous glucose is supplied. After delivery, the baby depletes his or her hepatic glycogen stores within 2–3 hours. The newborn is severely limited in his or her ability to use fat and protein as substrates to synthesize glucose. When total parenteral nutrition (TPN) is needed, the glucose infusion rate should be initiated at 4–6 mg/kg/min and advanced 1–2 mg/kg/min to a goal of 12 mg/kg/min.

Hypoglycemia

Clinical signs of hypoglycemia are nonspecific and subtle. Seizure and coma are the most common manifestations of severe hypoglycemia. Neonatal hypoglycemia is generally defined as a glucose level lower than 50 mg/dL.[3] Infants who are at high risk for developing hypoglycemia are those who are premature; SGA; or born to mothers with gestational diabetes, severe preeclampsia, or HELLP (hemolysis, elevated liver enzymes, low platelet count). Newborns who require surgical procedures are at particular risk of developing hypoglycemia; therefore, a 10% glucose infusion is typically started on admission to the hospital. Hypoglycemia is treated with an infusion of 1–2 mL/kg (4–8 mg/kg/min) of 10% glucose. If an emergency operation is required, concentrations of up to 25% glucose may be used. Traditionally, central venous access has been a prerequisite for glucose infusions exceeding 12.5%. During the first 36–48 hours after a major operation, it is common to see wide variations in serum glucose levels.

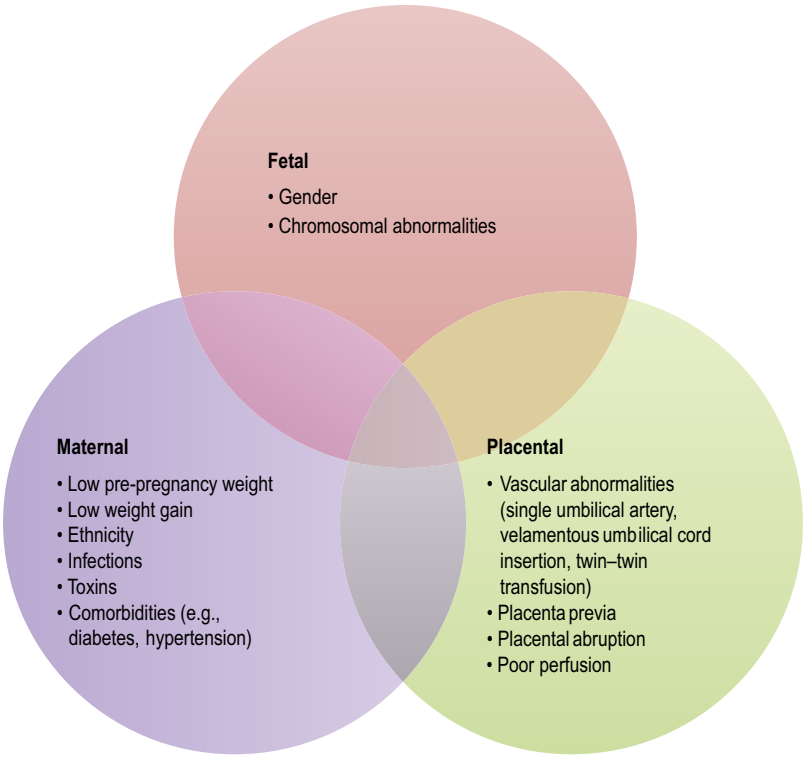

Fig. 1.1 Diagram of conditions associated with deviations in intrauterine growth. (Adapted from Simmons R. Abnormalities of fetal growth. In: Gleason CA, Devaskar SU, eds. Avery's Diseases of the Newborn. Philadelphia: Saunders; 2012. p. 51.[2])

Table 1.1 Clinical Criteria for Classification of Low Birth Weight Infants

Criteria	36 Weeks (Premature)	37–38 Weeks (Borderline Premature)	39 Weeks (Term)
Plantar creases	Rare, shallow	Heel remains smooth	Creases throughout sole
Size of breast nodule	Not palpable to <3 mm	4 mm	Visible (7 mm)
Head hair	Cotton wool quality		Silky; each strand can be distinguished
Earlobe	Shapeless, pliable with little cartilage		Rigid with cartilage
Testicular descent and scrotal changes	Small scrotum with rugal patch; testes not completely descended	Gradual descent	Enlarged scrotum creased with rugae; fully descended testes

Adapted from Avery ME, Villee D, Baker S, et al. Neonatology. In: Avery ME, First LR, eds. Pediatric Medicine. Baltimore: Williams & Wilkins; 1989. p. 148.

Hyperglycemia

Hyperglycemia is a common problem associated with the use of parenteral nutrition in very immature infants born at less than 30 weeks' gestation and birth weight of less than 1.1 kg. These infants are usually less than 3 days of age and are frequently septic.[4] The hyperglycemia appears to be associated with both insulin resistance and relative insulin deficiency, reflecting the prolonged catabolism seen in very low birth weight infants.[5] Historically, neonatal hyperglycemia has been linked to intraventricular hemorrhage, dehydration, and electrolyte losses; however, a causal relationship has not been established. Congenital hyperinsulinism refers to an inherited disorder that is the most common cause of recurrent hypoglycemia in infants. This group of disorders was previously referred to as nesidioblastosis, which is a misnomer, as nesidioblastosis is a term used to describe hyperinsulinemic hypoglycemia attributed to dysfunctional pancreatic beta cells with a characteristically abnormal histologic appearance.

CALCIUM

Calcium is actively transported across the placenta. Of the total amount of calcium transferred across the placenta, 75% is observed after 28 weeks' gestation,[6] which partially accounts for the high incidence of hypocalcemia in preterm infants. Neonates are predisposed to hypocalcemia due to limited calcium stores, renal immaturity, and relative hypoparathyroidism secondary to suppression by high fetal calcium levels. Some infants are at further risk for neonatal calcium disturbances owing to the presence of genetic defects, pathologic intrauterine conditions, or birth trauma.[7] Hypocalcemia is defined as an ionized calcium level of less than 1.22 mmol/L (4.9 mg/dL).[8] At greatest risk for hypocalcemia are preterm infants, newborn surgical patients, and infants born to mothers with complicated pregnancies, such as those with diabetes or those receiving bicarbonate infusions. Calcitonin, which inhibits calcium mobilization from the bone, is increased in premature and asphyxiated infants.

Table 1.2 Estimation of Blood Volume

Group	Blood Volume (mL/kg)
Premature infants	85–100
Term newborns	85
>1 month	75
3 months to adult	70

Adapted from Rowe PC, ed. The Harriet Lane Handbook.11th ed. Chicago: Year Book Medical; 1987. p. 25.

Signs of hypocalcemia are similar to those of hypoglycemia and may include jitteriness, seizures, cyanosis, vomiting, and myocardial arrhythmias. Hypocalcemic infants have increased muscle tone, which helps differentiate infants with hypocalcemia from those with hypoglycemia. Symptomatic hypocalcemia is treated with 10% calcium gluconate administered intravenous at a dosage of 1–2 mL/kg (100–200 mg/kg) over 30 minutes while monitoring the electrocardiogram for bradycardia.[3] Asymptomatic hypocalcemia is best treated with calcium gluconate in a dose of 50 mg of elemental calcium/kg/day added to the maintenance fluid: 1 mL of 10% calcium gluconate contains 9 mg of elemental calcium. If possible, parenteral calcium should be given through a central venous line, as skin and soft tissue necrosis may occur should the peripheral IV infiltrate.

MAGNESIUM

Magnesium is actively transported across the placenta. Half of total body magnesium is in the plasma and soft tissues. Hypomagnesemia is observed with growth retardation, maternal diabetes, after exchange transfusions, and with hypoparathyroidism. Although the mechanisms by which magnesium and calcium interact are not clearly defined, they appear to be interrelated. The same infants at risk for hypocalcemia are also at risk for hypomagnesemia. Magnesium deficiency should be suspected and confirmed in an infant who has seizures that do not respond to calcium therapy. Emergent treatment consists of magnesium sulfate 25–50 mg/kg IV every 6 hours until normal levels are obtained.

BLOOD VOLUME

Total RBC volume is at its highest point at delivery. Estimations of blood volume for premature infants, term neonates, and infants are summarized in Table 1.2. By about 3 months of age, total blood volume per kilogram is nearly equal to adult levels as infants recover from their postpartum physiologic nadir. The newborn blood volume is affected by shifts of blood between the placenta and the baby before clamping the cord. Infants with delayed cord clamping (typically defined as greater than 1 minute after birth) have higher hemoglobin levels.[9] A hematocrit greater than 50% suggests placental transfusion has occurred. Although this effect on hemoglobin levels does not persist, iron stores are positively impacted up to 6 months of age by delayed cord clamping.[10]

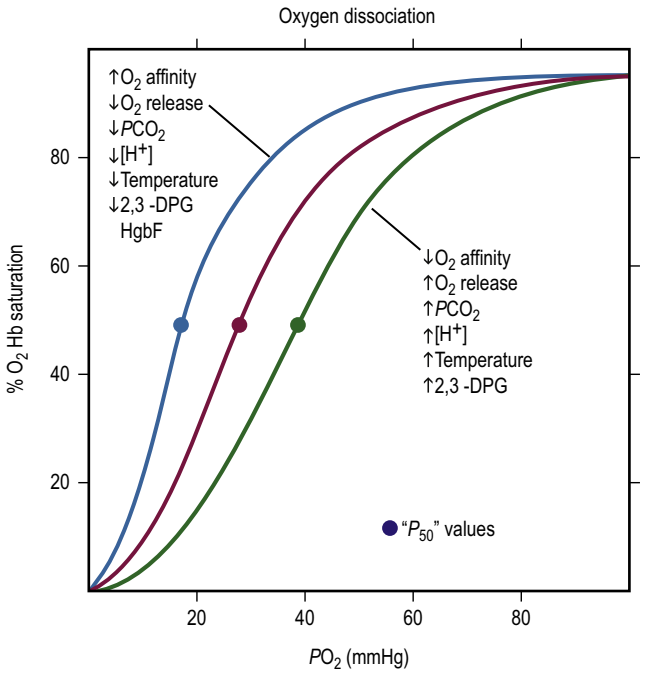

Fig. 1.2 The oxygen dissociation curve of normal adult blood is shown in red. The P_{50}, the oxygen tension at 50% oxygen saturation, is approximately 27 mmHg. As the curve shifts to the right, the affinity of hemoglobin for oxygen decreases and more oxygen is released. Increases in PCO_2, temperature, 2,3-DPG, and hydrogen ion concentration facilitates the unloading of O_2 from arterial blood to the tissue. With a shift to the left, unloading of O_2 from arterial blood into the tissues is more difficult. Causes of a shift to the left are mirror images of those that cause a shift to the right: decreases in temperature, 2,3-DPG, and hydrogen ion concentration. (Modified from Glancette V, Zipursky A. Neonatal hematology. In: Avery GB, ed. Neonatology. Philadelphia: JB Lippincott; 1986. p. 663.)

Hemoglobin

At birth, nearly 80% of circulating hemoglobin is fetal (a2Aγ2F). When infant erythropoiesis resumes at about 2–3 months of age, most new hemoglobin is adult. When the oxygen level is 27 mmHg, 50% of the bound oxygen is released from adult hemoglobin (P_{50} = 27 mmHg). Reduction of the affinity of hemoglobin for oxygen allows more oxygen to be released into the tissues at a given oxygen level as shown in Fig. 1.2.

Fetal hemoglobin has a P_{50} value 6–8 mmHg lower than that of adult hemoglobin. This lower P_{50} value allows more efficient oxygen delivery from the placenta to the fetal tissues. The fetal hemoglobin equilibrium curve is shifted to the left of the normal adult hemoglobin equilibrium curve. Fetal hemoglobin binds less avidly to 2,3-diphosphoglycerate (2,3-DPG) compared with adult hemoglobin, causing a decrease in P_{50}.[11] This is somewhat of a disadvantage to the newborn because lower peripheral oxygen levels are needed before oxygen is released from fetal hemoglobin. By 4–6 months of age in a term infant, the hemoglobin equilibrium curve gradually shifts to the right and the P_{50} value approximates that of a normal adult.

Polycythemia

A central venous hemoglobin level greater than 22 g/dL or a hematocrit value greater than 65% during the first

week of life is defined as polycythemia. After the central venous hematocrit value reaches 65%, further increases result in rapid exponential increases in blood viscosity. Neonatal polycythemia occurs in infants of diabetic mothers, infants of mothers with toxemia of pregnancy, or SGA infants. Polycythemia is treated using a partial exchange of the infant's blood with fresh whole blood or 5% albumin. This is frequently done for hematocrit values greater than 65%.

ANEMIA

Anemia present at birth is due to hemolysis, blood loss, or decreased erythrocyte production.

Hemolytic Anemia

Hemolytic anemia is most often a result of placental transfer of maternal antibodies that are destroying the infant's erythrocytes. This can be determined by the direct Coombs test. The most common severe anemia is Rh incompatibility. Hemolytic disease in the newborn produces jaundice, pallor, and hepatosplenomegaly. The most severely affected fetuses manifest hydrops. This massive edema is not strictly related to the hemoglobin level of the infant. ABO incompatibility frequently results in hyperbilirubinemia, but rarely causes anemia.

Congenital infections, hemoglobinopathies (sickle cell disease), and thalassemias produce hemolytic anemia. In a severely affected infant with a positive-reacting direct Coombs test result, a cord hemoglobin level less than 10.5 g/dL, or a cord bilirubin level greater than 4.5 mg/dL, immediate exchange transfusion is indicated. For less severely affected infants, exchange transfusion is indicated when the total indirect bilirubin level is greater than 20 mg/dL.

Hemorrhagic Anemia

Significant anemia can develop from hemorrhage that occurs during placental abruption. Internal bleeding (intraventricular, subgaleal, mediastinal, intra-abdominal) in infants can also often lead to severe anemia. Usually, hemorrhage occurs acutely during delivery, with the baby occasionally requiring a transfusion. Twin–twin transfusion reactions can produce polycythemia in one baby and profound anemia in the other. Severe cases can lead to death in the donor and hydrops in the recipient.

Anemia of Prematurity

Decreased RBC production frequently contributes to anemia of prematurity. Erythropoietin is not released until a gestational age of 30–34 weeks has been reached. These preterm infants have large numbers of erythropoietin-sensitive RBC progenitors. Research has focused on the role of recombinant erythropoietin (epoetin alpha) in treating anemia in preterm infants.[9–11] Successful increases in hematocrit levels using epoetin may obviate the need for blood transfusions and reduce the risk of blood borne infections and reactions. Studies suggest that routine use of epoetin is probably helpful for very low birth weight infants (<750 g), but its regular use for other preterm infants is not likely to significantly reduce the transfusion rate.[12–14]

Table 1.3 Causes of Prolonged Indirect Hyperbilirubinemia

Breast milk jaundice	Pyloric stenosis
Hemolytic disease	Crigler–Najjar syndrome
Hypothyroidism	Extravascular blood

Data from Maisels MJ. Neonatal jaundice. In: Avery GB, ed. Neonatology. Pathophysiology and Management of the Newborn. Philadelphia: JB Lippincott; 1987. p. 566.

JAUNDICE

In the hepatocyte, bilirubin created by hemolysis is conjugated to glucuronic acid and rendered water soluble. Conjugated (also known as direct) bilirubin is excreted in bile. Unconjugated bilirubin interferes with cellular respiration and is toxic to neural cells. Subsequent neural damage is termed *kernicterus* and produces athetoid cerebral palsy, seizures, sensorineural hearing loss, and, rarely, death.

The newborn's liver has a metabolic excretory capacity for bilirubin that is not equal to its task. Even healthy full-term infants usually have an elevated unconjugated bilirubin level. This peaks about the third day of life at approximately 6.5–7.0 mg/dL and does not return to normal until the tenth day of life. A total bilirubin level greater than 7 mg/dL in the first 24 hours or greater than 13 mg/dL at any time in full-term newborns often prompts an investigation for the cause. Breast-fed infants usually have serum bilirubin levels 1–2 mg/dL greater than formula-fed babies. Various factors have been associated with breast milk jaundice including substances in breast milk (e.g., steroids, fats, cytokines, β-glucuronidase, and epidermal growth factor), difficulties with breast-feeding, and infant weight loss. However, new studies also implicate differences in extrahepatic UDP-glucuronosyltransferase 1A1.[15,16] The common causes of prolonged indirect hyperbilirubinemia are listed in Table 1.3.

Pathologic jaundice within the first 36 hours of life is usually due to excessive production of bilirubin. Hyperbilirubinemia is managed based on the infant's weight. Although specific cutoffs defining the need for therapy have not been universally accepted, the following recommendations are consistent with most practice patterns.[17] Phototherapy is initiated for newborns: (1) less than 1500 g, when the serum bilirubin level reaches 5 mg/dL; (2) 1500–2000 g, when the serum bilirubin level reaches 8 mg/dL; or (3) 2000–2500 g, when the serum bilirubin level reaches 10 mg/dL. Formula-fed term infants without hemolytic disease are treated by phototherapy when levels reach 13 mg/dL. For hemolytic-related hyperbilirubinemia, phototherapy is recommended when the serum bilirubin level exceeds 10 mg/dL by 12 hours of life, 12 mg/dL by 18 hours, 14 mg/dL by 24 hours, or 15 mg/dL by 36 hours.[18] An absolute bilirubin level that triggers exchange transfusion is still not established, but most exchange transfusion decisions are based on the serum bilirubin level and its rate of rise.

RETINOPATHY OF PREMATURITY

Retinopathy of prematurity (ROP) develops during the active phases of retinal vascular development from the 16th week of gestation. In full-term infants the retina is fully developed and ROP cannot occur. The exact causes are unknown, but oxygen exposure (greater than 93–95%), low birth weight, and extreme prematurity are risk factors that have been demonstrated.[19,20] The risk and extent of ROP are probably related to the degree of vascular immaturity and abnormal retinal angiogenesis mediated to a large extent through vascular endothelial growth factor in response to hypoxia.[21] In the United States, ROP is found in 0.17% of all live births and 1.9% of premature infants in large neonatal units.[22,23] Retrolental fibroplasia (RLF) is the pathologic change observed in the retina and overlying vitreous after the acute phases of ROP subsides. Treatment of ROP with laser photocoagulation has been shown to have the added benefit of superior visual acuity and less myopia when compared with cryotherapy in long-term follow-up studies.[24–27] The American Academy of Pediatrics' guidelines recommend a screening examination for all infants who received oxygen therapy who weigh less than 1500 g and were born at less than 32 weeks' gestation, and selected infants with a birth weight between 1500 and 2000 g or gestational age of more than 32 weeks with an unstable clinical course, including those requiring cardiorespiratory support.[28]

THERMOREGULATION

Newborns have difficulty maintaining body temperature due to their relatively large surface area, poor thermal regulation, and small mass to act as a heat sink. Heat loss may occur as a result of: (1) evaporation (wet newborn); (2) conduction (skin contact with cool surface); (3) convection (air currents blowing over newborn); and (4) radiation (non-contact loss of heat to cooler surface, which is the most difficult factor to control). Thermoneutrality is the range of ambient temperatures at which the newborn can maintain a normal body temperature with a minimal metabolic rate by vasomotor control. The *critical temperature* is the temperature that requires adaptive metabolic responses to the cold in an effort to replace lost heat. Infants produce heat by increasing metabolic activity by shivering like an adult, nonshivering thermogenesis, and futile cycling of ions in skeletal muscle.[29] Brown adipose tissue (BAT) may be involved in thermoregulatory feeding and sleep cycles in the infant, with an increase in body temperature signaling an increase in metabolic demand.[30] The uncoupling of mitochondrial respiration that occurs in BAT, where energy is not conserved in ATP but rather is released as heat, may be rendered inactive by vasopressors, anesthetic agents, and nutritional depletion.[31–33] Failure to maintain thermoneutrality leads to serious metabolic and physiologic consequences. Double-walled incubators offer the best thermoneutral environment, whereas radiant warmers cannot prevent convection heat loss and lead to higher insensible water loss. In the operating room, special care must be exercised to maintain the neonate's body temperature in the normal range.

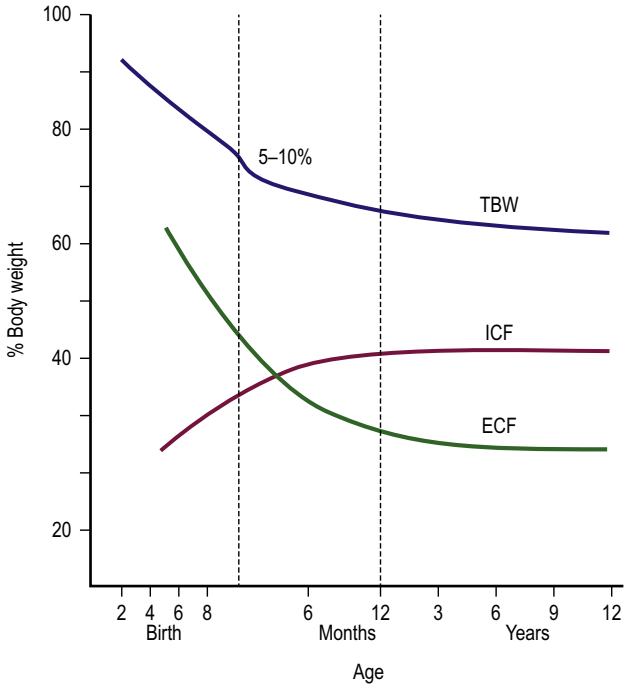

Fig. 1.3 Friss–Hansen's classic chart relating total body weight (TBW) and extracellular (ECF) and intracellular (ICF) fluid to percentage of body weight, from early gestation to adolescence. (Adapted from Welch KJ, Randolph JG, Ravitch MM, et al., eds. Pediatric Surgery. 4th ed. Chicago: Year Book Medical; 1986. p. 24.)

Fluids and Electrolytes

At 12 weeks of gestation, the fetus has a total body water content that is 94% of body weight. This amount decreases to 80% by 32 weeks' gestation and 78% by term (Fig. 1.3). A further 3–5% reduction in total body water content occurs in the first 3–5 days of life. Body water continues to decline and reaches adult levels (approximately 60% of body weight) by 1½ years of age. Extracellular water also declines by 1–3 years of age. Premature delivery requires the newborn to complete both fetal and term water unloading tasks. Surprisingly, the premature infant can complete fetal water unloading by 1 week following birth. Postnatal reduction in extracellular fluid volume has such a high physiologic priority that it occurs even in the presence of relatively large variations of fluid intake.[34]

GLOMERULAR FILTRATION RATE AND EARLY RENAL FUNCTION

The glomerular filtration rate (GFR) of newborns is slower than that of adults.[35] From 21 mL/min/1.73 m^2 at birth in the term infant, GFR quickly increases to 60 mL/min/1.73 m^2 by 2 weeks of age. GFR reaches adult levels by 18 months to 2 years of age. A preterm infant has a GFR that is only slightly slower than that

Table 1.4 Newborn Fluid Volume Requirements (mL/kg/24 h) for Various Surgical Conditions

Group	Day 1	Day 2	Day 3
Moderate surgical conditions (e.g., colostomies, laparotomies for intestinal atresia, Hirschsprung disease)	80 ± 25	80 ± 30	80 ± 30
Severe surgical conditions (e.g., gastroschisis, midgut volvulus, meconium peritonitis)	140 ± 45	90 ± 20	80 ± 15
Necrotizing enterocolitis with perforation	145 ± 70	135 ± 50	130 ± 40

of a full-term infant. In addition to this difference in GFR, the concentrating capacity of the preterm and the full-term infant is well below that of the adult. An infant responding to water deprivation increases urine osmolarity to a maximum of 600 mOsm/kg. This is in contrast to the adult, whose urine concentration can reach 1200 mOsm/kg. It appears that the difference in concentrating capacity is due to the insensitivity of the collecting tubules of the newborn to antidiuretic hormone. Although the newborn cannot concentrate urine as efficiently as the adult, the newborn can excrete very dilute urine at 30–50 mOsm/kg. Newborns are unable to excrete excess sodium, an inability thought to be due to a tubular defect. Term babies are able to conserve sodium, but premature infants are considered "salt wasters" because they have an inappropriate urinary sodium excretion, even with restricted sodium intake.

NEONATAL FLUID REQUIREMENTS

To estimate fluid requirements in the newborn requires an understanding of: (1) any preexisting fluid deficits or excesses, (2) metabolic demands, and (3) losses. Because these factors change quickly in the critically ill newborn, frequent adjustments in fluid management are necessary (Table 1.4). Hourly monitoring of intake and output allows early recognition of fluid balance that will affect treatment decisions. This dynamic approach requires two components: (1) an initial hourly fluid intake that is safe and (2) a monitoring system to detect the patient's response to the treatment program selected. No "normal" urine output exists for a given neonate, yet one may generally target 1–2 mL/kg/h.

After administering the initial hourly volume for 4–8 hours, depending on the patient's condition, the newborn is reassessed by observing urine output and concentration. With these two factors, it is possible to determine the state of hydration of most neonates and their responses to the initial volume. In more difficult cases, changes in serial serum osmolarity and sodium (Na), creatinine, and blood urea nitrogen (BUN) levels, along with urine osmolarity and Na and creatinine levels, make it possible to assess the infant's response to the initial volume and to use fluid status to guide the fluid intake over the next 4–8 hours.

Illustrative Examples

Insufficient Fluid

During the first 8 hours postoperatively, a 1-kg premature infant has 0.3 mL/kg/h of urine output. Specific gravity is 1.025. Previous initial volume was 5 mL/kg/h. Serum BUN has increased from 4 mg/dL to 8 mg/dL; hematocrit value has increased from 35% to 37%, without transfusion.

This child is dehydrated. The treatment is to increase the hourly volume to 7 mL/kg/h for the next 4 hours and to monitor the subsequent urine output and concentration to reassess fluid status. Depending on the degree of dehydration and the child's underlying cardiopulmonary status, it may be prudent to bolus the child with 10–20 mL/kg of 0.9% normal saline—all the while carefully monitoring physiologic responsiveness.

Inappropriate Antidiuretic Hormone Response

During the first 8 hours postoperatively, a 3-kg newborn with congenital diaphragmatic hernia (CDH) has 0.2 mL/kg/h of urine output and a urine osmolarity of 360 mOsm/L. The previous fluid volume was 120 mL/kg/day (15 mL/h). The serum osmolarity has decreased from 300 mOsm/L preoperatively to 278 mOsm/L; BUN has decreased from 12 mg/dL to 8 mg/dL.

The inappropriate antidiuretic hormone response requires reduction in fluid volume from 120 mL/kg/day to 90 mL/kg/day for the next 4–8 hours. Repeat urine and serum measurements will allow for further adjustment of fluid administration.

Overhydration

A 3-kg baby, 24 hours following operative closure of gastroschisis, had an average urine output of 3 mL/kg/h for the past 4 hours. During that time period, the infant received fluids at a rate of 180 ml/kg/day. The specific gravity of the urine has decreased to 1.006; serum BUN is 4 mg/dL; hematocrit value is 30%, down from 35% preoperatively. The total serum protein concentration is 4.0 mg/dL, down from 4.5 mg/dL.

This child is overhydrated. The treatment is to decrease the fluids to 3 mL/kg/h for the next 4 hours and then to reassess urine output and concentration.

Renal Failure

A 5-kg infant with severe sepsis secondary to Hirschsprung enterocolitis has had a urine output of 0.1 mL/kg/h for the past 8 hours. The specific gravity is 1.012; serum sodium, 150; BUN, 25 mg/dL; creatinine, 1.5 mg/dL; urine sodium, 130; and urine creatinine, 20 mg/dL.

Fractional Na excretion (FE Na)

$$\text{FE Na} = \frac{\text{Ur Na} \times \text{Pl Cr}}{\text{Pl Na} \times \text{Ur Cr}} = \frac{130 \times 1.5}{150 \times 20}$$
$$= 193/3000 \times 100$$
$$= 6.5\ \% \text{ (normal = 2–3\% in newborns)}$$

FE Na less than 1% usually indicates a prerenal cause of oliguria, whereas greater than 3% usually implies a renal cause (e.g., acute tubular necrosis). This patient is in acute renal failure. The plan is to restrict fluids to insensible losses plus measured losses for the next 4 hours and to then reassess the plan using both urine and serum studies. Of note, while the FE urea may be a better predictor of prerenal failure in this population, both FE urea and the FE Na have limited utility in neonates, reflecting the relative immaturity of neonatal renal function.[36]

Cardiovascular System of the Newborn

In the first moments of extrauterine life, the transition from fetal to neonatal circulation begins. An appreciation of this transition is imperative to the care of neonates. The changes occur primarily through shifts in vascular resistance and increased partial pressure of oxygen in the arterial blood (PaO_2).[37–39] With the neonate's first breath, the lungs began inflating. Simultaneously, the relatively low fetal PaO_2 (maximum of 30–35 mmHg from the umbilical vein) rises with the switch from placental to pulmonary gas exchange. The combination of these changes causes a substantial decrease in pulmonary vascular resistance. In addition, with the removal of the placenta from circulation, systemic vascular resistance increases.

Fetal circulation is marked by three prominent structures: the foramen ovale, ductus arteriosus, and ductus venosus. The foramen ovale shunts blood from the right atrium into the left atrium, largely bypassing the pulmonary circulation. With an increase in blood flow from the pulmonary system returning to the left atrium after birth, the flap of the foramen ovale functionally closes in most infants by 3 months of age. The ductus arteriosus serves as a conduit from the pulmonary artery to the descending aorta. Flow is reversed after birth due to higher systemic vascular resistance and lower pulmonary vascular resistance. The ductus arteriosus closes within 24 hours after birth primarily because of vasoconstriction secondary to higher PaO_2 as well as the absence of placental prostaglandins. The ductus venosus connects the umbilical vein to the inferior vein cava and serves as a route to divert approximately half of the blood flow away from the fetal liver. With increased oxygenation after delivery, the ductus venosus occludes and closes.[40] Of note, congenital cardiac defects and prematurity can lead to alterations in the normal circulatory transition.

PULMONARY SYSTEM OF THE NEWBORN

Maturation of the lungs is generally divided into five periods:

- Embryonic phase (begins approximately week 3)
- Pseudoglandular phase (5–17 weeks)
- Canalicular phase (16–25 weeks)
- Terminal saccular phase (24 weeks to full-term birth)
- Alveolar phase (late fetal phase to childhood).

Pulmonary development begins in the third week (embryonic phase) when a ventral diverticulum develops off the foregut (laryngotracheal groove), initiating tracheal development. During the pseudoglandular phase, all of the major elements of the lung form except those involved in gas exchange. The dichotomous branching of the bronchial tree that develops during the fourth week from the primitive trachea is usually completed by 17 weeks' gestation. Fetuses born during this phase are unable to survive because respiration is not possible. In the canalicular phase, respiration is made possible because thin-walled terminal sacs (primordial alveoli) have developed at the ends of the respiratory bronchioles and the lung tissue is well vascularized. No actual alveoli are seen until 24–26 weeks' gestation, during the terminal saccular phase. The air–blood surface area for gas diffusion is limited should the fetus be delivered at this age. The terminal saccular phase is defined by the establishment of the blood–air barrier that allows gas exchange for the survival of the fetus should it be born prematurely. Between 24 and 28 weeks, the cuboidal and columnar cells flatten and differentiate into type I (lining cells) and/or type II (granular) pneumocytes. Between 26 and 32 weeks of gestation, terminal air sacs begin to give way to air spaces. At the same time, the phospholipids that constitute pulmonary surfactant begin to line the terminal lung air spaces. Surfactant is produced by type II pneumocytes and is extremely important in maintaining alveolar stability. During the alveolar phase, further budding of these air spaces occurs and alveoli become numerous, a process that continues postnatally until the age of 3–8 years.[41]

The change in the ratio of the amniotic phospholipids (lecithin: sphingomyelin) is used to assess fetal lung maturity. A ratio greater than 2 is considered compatible with mature lung function. Absence of adequate surfactant leads to HMD or respiratory distress syndrome (RDS). HMD is present in 10% of premature infants. Other conditions associated with pulmonary distress in the newborn include delayed fetal lung absorption, meconium aspiration syndrome, intrapartum pneumonia, and developmental structural anomalies (e.g., CDH and congenital lobar emphysema). In all of these conditions, endotracheal intubation and mechanical ventilation may be required for hypoxia, CO_2 retention, or apnea. Ventilator options and management depend on the clinical context and are discussed further in Chapter 7.

To accelerate fetal lung maturity, a maternal dose of corticosteroids is the standard of care of threatened preterm delivery.[42] This therapy reduces the incidence of perinatal death as well as RDS. Proposed pathways for the effect of corticosteroids on lung maturity include stimulation of surfactant production through enzymatic induction, increasing pulmonary blood flow, and increasing air space volume by decreasing perialveolar tissue volume.[43,44] Studies are ongoing to investigate concerns regarding the short- and long-term effects of antenatal corticosteroid administration as well as the consequences of repeated doses.[45,46]

SURFACTANT

The development of exogenous surfactant in the 1990s significantly advanced the field of neonatology, resulting in reductions in the rates of neonatal mortality. Surfactant deficiency is the major cause of HMD. Surfactant replacement therapy reduces the surface tension on the inner surface of the alveoli, preventing the alveoli from collapsing during expiration and thereby improving air exchange. Three exogenous surfactants are available: (1) surfactant derived from bovine or porcine lung, (2) synthetic surfactant without protein components, and (3) synthetic surfactant containing protein components. A human-derived surfactant has been tested but is not currently in use.

Table 1.5 Adverse Effects of Surfactant Therapy

Acute Adverse Effects of Surfactant Therapy	Transient Adverse Effects of Surfactant Therapy	Minimal to Small Risk	No Differences Between Placebo and Surfactant Treated Infants
▪ Transient hypoxia and bradycardia from airway obstruction	▪ Decrease in blood pressure	▪ Pulmonary hemorrhage	▪ Neurodevelopment outcomes
	▪ Decrease in cerebral blood flow velocity		▪ Respiratory outcomes
			▪ Physical growth
▪ Reflux of surfactant into the pharynx	▪ Decrease in cerebral activity on EEG		▪ Intraventricular hemorrhage
▪ Mucous plugging of the endotracheal tube			

EEG, electroencephalogram.

The most efficacious administration method is currently under investigation. The standard approach is to instill aliquots into an endotracheal tube. The indications for the use of surfactant include: (1) intubated infants with RDS, (2) intubated infants with meconium aspiration syndrome requiring more than 50% oxygen, (3) intubated infants with pneumonia and an oxygen index great than 15, and (4) intubated infants with pulmonary hemorrhage who have clinically deteriorated. Its efficacy is uncertain in neonates with pulmonary hemorrhage and pneumonia. Worse outcomes are associated when surfactant is used in CDH.[47,48]

The acute pulmonary effects of surfactant therapy are improved lung function and alveolar expansion leading to improved oxygenation, which results in a reduction in the need for mechanical ventilation and extracorporeal oxygenation.[49-51]

Two meta-analyses support the use of surfactant therapy in infants with RDS to reduce air leak syndromes, pneumothorax, bronchopulmonary dysplasia (BPD), pulmonary interstitial emphysema, and mortality.[52,53] The INSURE (INtubate, SURfactant, Extubate) technique consists of administration of surfactant followed by extubation within 1 hour to nasal continuous positive airway pressure (nCPAP). Another randomized trial demonstrated the reduced mortality and air leaks for infants assigned to early surfactant treatment versus nCPAP alone.[54] In large trials that reflect the current practice of treating infants at risk for the development of RDS (administration of maternal steroids and the routine stabilization on nCPAP), the selective use of surfactant in infants with established RDS demonstrates a decreased risk of chronic lung disease or death when compared with infants who are more aggressively treated with prophylactic administration of surfactant.[55,56]

Several adverse outcomes have been associated with the use of surfactant (Table 1.5). Intraventricular hemorrhage is one of the most worrisome potential side effects. However, meta-analyses of multiple trials have not shown a statistically significant increase in this risk.[52,53]

Monitoring

Continuous monitoring of physiologic indices provides data to assess the response to therapy. In retrospect, many episodes of "sudden deterioration" in critically ill patients are viewed as changes in the clinical condition that had been occurring for some time.

ARTERIAL BLOOD GASES AND DERIVED INDICES

Arterial oxygen tension (PaO_2) is measured most commonly by obtaining an arterial blood sample and by measuring the partial pressure of oxygen with a polarographic electrode. In the term newborn, the general definition for hypoxia is a PaO_2 less than 55 mmHg, whereas hyperoxia is greater than 80 mmHg.

Capillary blood samples are "arterialized" by topical vasodilators or heat to increase blood flow to a peripheral site. Blood flowing sluggishly and exposed to atmospheric oxygen falsely raises the PaO_2 from a capillary sample, especially in the 40–60 mmHg range.[57] Capillary blood pH and carbon dioxide tension (PCO_2) correlate well with arterial samples, unless perfusion is poor. PaO_2 is least reliable when determined by capillary blood gas. In patients receiving oxygen therapy in which arterial PaO_2 exceeds 60 mmHg, the capillary PaO_2 correlates poorly with the arterial measurement.[58,59]

In newborns, umbilical artery catheterization provides arterial access. The catheter tip should rest at the level of the diaphragm or below L3. The second most frequently used arterial site is the radial artery. Complications of arterial blood sampling include repeated blood loss and anemia. Distal extremity or organ ischemia from thrombosis or arterial injury is rare but can occur. Changes in oxygenation are such that intermittent blood gas sampling may miss critical episodes of hypoxia or hyperoxia. Due to the drawbacks of ex vivo monitoring, several in vivo monitoring systems have been used.

PULSE OXIMETRY

The noninvasive determination of oxygen saturation (SaO_2) gives moment-to-moment information regarding the availability of O_2 to the tissues. If the PaO_2 is plotted against the oxygen saturation of hemoglobin, the S-shaped hemoglobin dissociation curve is obtained (see Fig. 1.2). From this curve, it is evident that hemoglobin is 50% saturated at 27 mmHg PaO_2 and 90% saturated at 50 mmHg. Pulse oximetry has a rapid (5–7 seconds) response time, requires no calibration, and may be left in place continuously.

Pulse oximetry is not possible if the patient is in shock, has peripheral vasospasm, or has vascular constriction due to hypothermia. Inaccurate readings may occur in the presence of jaundice, direct high-intensity light, dark skin pigmentation, and greater than 80% fetal hemoglobin.

Oximetry is not a sensitive guide to gas exchange in patients with high PaO_2 due to the shape of the oxygen dissociation curve. On the upper horizontal portion of the curve, large changes in PaO_2 may occur with little change in SaO_2. For instance, an oximeter reading of 95% could represent a PaO_2 between 60 and 160 mmHg.

A study comparing pulse oximetry with PaO_2 from indwelling arterial catheters has shown that SaO_2 greater than or equal to 85% corresponds to a PaO_2 greater than 55 mmHg, and saturations less than or equal to 90% correspond with a PaO_2 less than 80 mmHg.[60] Guidelines for monitoring infants using pulse oximetry have been suggested for the following three conditions:

1. In the infant with acute respiratory distress without direct arterial access, saturation limits of 85% (lower) and 92% (upper) should be set.
2. In the older infant with chronic respiratory distress who is at low risk for ROP, the upper saturation limit may be set at 95%; the lower limit should be set at 87% to avoid pulmonary vasoconstriction and pulmonary hypertension.
3. As the concentration of fetal hemoglobin in newborns affects the accuracy of pulse oximetry, infants with arterial access should have both PaO_2 and SaO_2 monitored closely. A graph should be kept at the bedside, documenting the SaO_2 each time the PaO_2 is measured. Limits for the SaO_2 alarm can be changed because the characteristics of this relationship change.

CARBON DIOXIDE TENSION

Arterial carbon dioxide tension ($PaCO_2$) is a direct reflection of gas exchange in the lungs and metabolic rate. In most clinical situations, changes in $PaCO_2$ are due to changes in ventilation. For this reason, serial measurement of $PaCO_2$ is a practical method to assess the adequacy of ventilation. It is also possible to monitor $PaCO_2$ and pH satisfactorily with venous or capillary blood samples. Therefore, many infants with respiratory insufficiency no longer require arterial catheters for monitoring.

END-TIDAL CARBON DIOXIDE

Measuring expired CO_2 by capnography provides a noninvasive means of continuously monitoring alveolar PCO_2. Capnometry measures CO_2 by an infrared sensor either placed in-line between the ventilator circuit and the endotracheal tube or off to the side of the air flow, both of which are applicable only to the intubated patient. A comparative study of end-tidal carbon dioxide in critically ill neonates demonstrated that both sidestream and mainstream end-tidal carbon dioxide measurements approximated $PaCO_2$.[61] When the mainstream sensor was inserted into the breathing circuit, the $PaCO_2$ increased an average of 2 mmHg.

CENTRAL VENOUS CATHETER

Indications for central venous catheter placement include: (1) hemodynamic monitoring, (2) inability to establish other venous access, (3) TPN, and (4) infusion of inotropic drugs or other medications that cannot be given peripherally. Measuring central venous pressure (CVP) to monitor volume status is frequently used in the resuscitation of a critically ill patient. A catheter placed in the superior vena cava or right atrium measures the filling pressure of the right side of the heart, which usually reflects left atrial and filling pressure of the left ventricle. Often, a wide discrepancy exists between left and right atrial pressure if pulmonary disease, overwhelming sepsis, or cardiac anomalies are present. Positive-pressure ventilation, pneumothorax, abdominal distention, or pericardial tamponade all elevate CVP.

PULMONARY ARTERY

The pulmonary artery pressure catheter has altered the care of the child with severe cardiopulmonary derangement by allowing direct measurement of cardiovascular variables at the bedside. With this catheter, it is possible to monitor CVP, pulmonary artery pressure, pulmonary wedge pressure, and cardiac output. The catheter is usually placed by percutaneous methods (as in the adult), except in the smallest pediatric patient in whom a cutdown is sometimes required.

When the tip of the catheter is in a distal pulmonary artery and the balloon is inflated, the resulting pressure is generally an accurate reflection of left atrial pressure because the pulmonary veins do not have valves. This pulmonary "wedge" pressure represents left ventricular filling pressure, which is used as a reflection of preload. The monitors display phasic pressures, but treatment decisions are made based on the electronically derived mean CVP. A low pulmonary wedge pressure suggests that blood volume must be expanded. A high or normal pulmonary wedge pressure in the presence of continued signs of shock suggests left ventricular dysfunction.

Cardiac output is usually measured in liters per minute. Cardiac index represents the cardiac output divided by the body surface area. The normalized cardiac index allows the evaluation of cardiac performance without regard to body size. The normal value for cardiac index is between 3.5 and 4.5 L/min/m^2. The determination of cardiac output by the thermodilution technique is possible with a Swan–Ganz pulmonary artery catheter. Accurate cardiac output determination depends on rapid injection, accurate measurement of the injectant temperatures and volume, and absence of shunting. Because ventilation affects the flow into and out of the right ventricle, three injections should be made at a consistent point in the ventilatory cycle, typically at end-expiration.

Another study concluded that using right heart catheters in treating critically ill adult patients resulted in an increased mortality.[62] However, a consensus committee report has documented the continued safety and efficacy of right heart catheters in the care of critically ill children.[63] A newer technique of deriving some of these data employs femoral arterial access and is gaining popularity in the pediatric intensive care unit: transcardiopulmonary thermodilution monitoring device (pulse contour cardiac output [PCCO]).

A proprietary PiCCO® device has been developed and employs a standard central venous catheter and a proprietary thermistor-tipped arterial catheter to assess hemodynamic parameters via transpulmonary thermodilution. Manual calibration is required and must be performed frequently (every hour) for reasonably accurate data.[64] It is recommended to recalibrate the curve after interventions

are performed.[65] This device may give incorrect thermodilution measurements if blood is either extracted from or infused back into the cardiopulmonary circulation, as seen with an intracardiac shunt, aortic stenosis, lung embolism, and extracorporeal membrane oxygenation (ECMO).[66]

VENOUS OXIMETRY

Mixed venous oxygen saturation (SvO_2) is an indicator of the adequacy of oxygen supply and demand in perfused tissues. Oxygen consumption is defined as the amount of oxygen consumed by the tissue as calculated by the Fick equation:

O_2 consumption = Cardiac output × (Arterial − venous oxygen content difference)

Reflectance spectrophotometry is currently used for continuous venous oximetry. Multiple wavelengths of light are transmitted at a known intensity by means of fiber optic bundles in a special pulmonary artery or right atrial catheter. The light is reflected by RBCs flowing past the tip of the catheter. The wavelengths of light are chosen so that both oxyhemoglobin and deoxyhemoglobin are measured to determine the fraction of hemoglobin saturated with oxygen. The system requires either in vitro calibration by reflecting light from a standardized target that represents a known oxygen saturation or in vivo calibration by withdrawing blood from the pulmonary artery catheter and measuring the saturation by laboratory co-oximetry.

Mixed venous oxygen saturation values within the normal range (68–77%) indicate a normal balance between oxygen supply and demand, provided that vasoregulation is intact and distribution of peripheral blood flow is normal. Values greater than 77% are most commonly associated with syndromes of vasoderegulation, such as sepsis. Uncompensated changes in O_2 saturation, hemoglobin level, or cardiac output lead to a decrease in SvO_2. A sustained decrease in SvO_2 greater than 10% should lead to measuring SaO_2, hemoglobin level, and cardiac output to determine the cause of the decline.[67] The most common sources of error in measuring SvO_2 are calibration and catheter malposition. The most important concept in SvO_2 monitoring is the advantage of continuous monitoring, which allows early warning of a developing problem.[68]

Although most clinical experience has been with pulmonary artery catheters, right atrial catheters are more easily inserted and may thus provide better information to detect hemodynamic deterioration earlier and permit more rapid treatment of physiologic derangements.[69] A study has shown that, when oxygen consumption was monitored and maintained at a consistent level, the right atrial venous saturation was found to be an excellent monitor.[70]

Shock

Shock is a state in which the cardiac output is insufficient to deliver adequate oxygen to meet metabolic demands of the tissues. Cardiovascular function is determined by preload, cardiac contractility, heart rate, and afterload. Shock may be classified broadly as hypovolemic, cardiogenic, or distributive (systemic inflammatory response syndrome [SIRS]—septic or neurogenic).

HYPOVOLEMIC SHOCK

In infants and children, most shock situations are the result of reduced preload secondary to fluid loss, such as from diarrhea, vomiting, or blood loss from trauma. Preload is predominantly a function of blood volume. In most clinical situations, right atrial pressure or CVP is the index of cardiac preload. In situations in which left ventricular or right ventricular compliance is abnormal or in certain forms of congenital heart disease, right atrial pressure may not correlate well with left atrial pressure.

Hypovolemia results in decreased venous return to the heart. Preload is reduced, cardiac output falls, and the overall result is a decrease in tissue perfusion. The first step in treating all forms of shock is to correct existing fluid deficits. Inotropic drugs should not be initiated until adequate intravascular fluid volume has been established. The speed and volume of the infusate are determined by the patient's responses, particularly changes in blood pressure, pulse rate, urine output, and CVP. Shock resulting from acute hemorrhage is treated with the administration of 20 mL/kg of Ringer's lactate solution or normal saline as fluid boluses. If the patient does not respond, a second bolus of crystalloid is given. Type-specific or cross-matched blood is given to achieve an $SvO2$ of 70%. In newborns with a coagulopathy, fresh frozen plasma or specific factors are provided as the resuscitation fluid.

The rate and volume of the resuscitation fluid are adjusted based on feedback data obtained from monitoring the effects of the initial resuscitation. After the initial volume is given, the adequacy of replacement is assessed by monitoring urine output, urine concentration, plasma acidosis, oxygenation, arterial pressure, CVP, and pulmonary wedge pressure, if indicated. When cardiac failure is present, continued vigorous delivery of large volumes of fluid not matched by cardiac output may cause further increases in preload to the failing myocardium and accelerate the downhill course. In this setting, inotropic agents are given while monitoring cardiac and pulmonary function, as previously discussed.

CARDIOGENIC SHOCK

Myocardial contractility is usually expressed as the ejection fraction that indicates the proportion of left ventricular volume that is pumped. Myocardial contractility is reduced with hypoxemia and acidosis. Inotropic drugs increase cardiac contractility. Inotropes are most effective when hypoxemia and acidosis are corrected. In cases of fluid-refractory shock and cardiogenic shock, inotropic drugs are necessary. Traditionally, administration of inotropes requires the adjunct of central venous access. However, initial administration of pressors through peripheral IVs may be prudent.

Adrenergic receptors are important in regulating calcium flux, which, in turn, is important in controlling myocardial contractility. The α and β receptors are proteins present in the sarcolemma of myocardial and vascular smooth muscle cells. The β_1 receptors are predominantly

Table 1.6 Vasoactive Medications Commonly Used in the Newborn

Vasoactive Agent	Principal Modes of Action	Major Hemodynamic Effects	Administration and Dosage	Indications
Epinephrine	α and β agonist	Increases heart rate and myocardial contractility by activating β_1 receptors	0.1 mL/kg of 1:10,000 solution given IV intracardial, *or* endotracheal 0.05–1.0 μg/kg/min IV	Cardiac resuscitation; short-term use when severe heart failure resistant to other drugs
Norepinephrine	α and β agonist	Increases BP by vasoconstriction with its greater action on β receptors	20–100 ng/kg/min initially, up to 1.0 μg/kg/min as base	Shock state with high cardiac output and low systemic vascular resistance
Vasopressin	ADH agonist in arterioles	May replace basal vasopressin levels in cases of severe hypotension	0.018–0.12 units/kg/h used as a rescue treatment	Restoration of vascular tone in vasodilatory shock
Dopamine, low dose	Stimulates dopamine receptors	Decrease in vascular resistance in splanchnic, renal, and cerebral vessels	<5 μg/kg/min IV	Useful in managing cardiogenic or hypovolemic shock or after cardiac surgery
Dopamine, intermediate dose	Stimulates β_1 receptors; myocardial	Inotropic response	5–10 μg/kg/min IV	Blood pressure unresponsive to low dose
Dopamine, high dose	Stimulates α receptors	Increased peripheral and renal vascular resistance	10–20 μg/kg/min IV	Septic shock with low systemic vascular resistance
Dobutamine	Synthetic β_1 agonist in low doses; α and β_2 effects in higher doses	Increased cardiac output, increased arterial pressure; less increase in heart rate than with dopamine	1–10 μg/kg/min IV	Useful alternative to dopamine if increase in heart rate undesirable
Isoproterenol	β_1 and β_2 agonist	Increased cardiac output by positive inotropic and chronotropic action and increase in venous return; systemic vascular resistance generally reduced; pulmonary vascular resistance generally reduced	0.5–10.0 μg/kg/min IV	Useful in low-output situations, especially when heart rate is slow
Sodium nitroprusside	Direct-acting vasodilator that relaxes arteriolar and venous smooth muscle	Afterload reduction; reduced arterial pressure	1–10 μg/kg/min IV (for up to ten minutes); 0.5–2.0 μg/kg/min IV	Hypertensive crisis; vasodilator therapy
Milrinone	Phosphodiesterase inhibitor relaxes arteriolar and venous smooth muscle via calcium/cyclic adenosine monophosphate	Increased cardiac output, slight decreased BP, increased oxygen delivery	75 μg/kg bolus IV, then 0.75–1.0 μg/kg/min IV	Useful as an alternative or in addition to dopamine (may act synergistically) if increased heart rate undesirable

ADH, antidiuretic hormone; *BP,* blood pressure; *IV,* intravenous.

Adapted from Lees MH, King DH. Cardiogenic shock in the neonate. Pediatr Rev. 1988;9:263; Yager P, Noviski N. Shock. Pediatrics in Review. 2010;21:311–318; and Piastra M, Luca E, Mensi S, et al. Inotropic and vasoactive drugs in pediatric ICU. Current Drug Targets. 2012;13:900–905.

in the heart and, when stimulated, result in increased contractility of myocardium. The β_2 receptors are predominately in respiratory and vascular smooth muscle. When stimulated, these receptors result in bronchodilation and vasodilation. The α_1-adrenergic receptors are located on vascular smooth muscle and result in vascular constriction when stimulated. The α_2 receptors are found mainly on prejunctional sympathetic nerve terminals. The concept of dopaminergic receptors has also been used to account for the cardiovascular effects of dopamine not mediated through α or β receptors. Activation of dopaminergic receptors results in decreased renal and mesenteric vascular resistance and, usually, increased blood flow. The most commonly used inotropic and vasoactive drugs are listed in Table 1.6.

Epinephrine

Epinephrine is an endogenous catecholamine with α- and β-adrenergic effects. At low doses, the β-adrenergic effect predominates. These effects include an increase in heart rate, cardiac contractility, cardiac output, and bronchiolar dilation. Blood pressure rises, in part, not only due to increased cardiac output but also due to increased peripheral vascular resistance, which occurs with higher doses as the α-adrenergic effects become predominant. Renal blood flow may increase slightly, remain unchanged, or decrease depending on the balance between greater cardiac output and changes in peripheral vascular resistance, which lead to regional redistribution of blood flow. Cardiac arrhythmias can be seen with use of epinephrine, especially at higher doses. Dosages for treating compromised cardiovascular function range from 0.05–1.0 μg/kg/min. Excessive doses of epinephrine can cause worsening cardiac ischemia and dysfunction from increased myocardial oxygen demand.

Isoproterenol

Isoproterenol is a β-adrenergic agonist. It increases cardiac contractility and heart rate, with little change in systemic vascular resistance (SVR). The peripheral vascular β-adrenergic effect and lack of a peripheral vascular α-adrenergic effect may allow reduction of left ventricular afterload. The intense chronotropic effect of isoproterenol produces tachycardia, which can limit its usefulness. Isoproterenol is administered IV at a dosage of 0.5–10.0 μg/kg/min.

Dopamine

Dopamine is an endogenous catecholamine with β-adrenergic, α-adrenergic, and dopaminergic effects. It is both a direct and an indirect β-adrenergic agonist. Dopamine elicits positive inotropic and chronotropic responses by direct interaction with the β receptor (direct effect) and by stimulating the release of norepinephrine from the sympathetic nerve endings, which interacts with the β receptor (indirect effect). At low dosages (<5 μg/kg/min), the dopaminergic effect of the drug predominates, resulting in reduced renal and mesenteric vascular resistance and further blood flow to these organs. The β-adrenergic effects become more prominent at intermediate dosages (5–10 μg/kg/min), producing a higher cardiac output. At relatively high dosages (10–20 μg/kg/min), the α-adrenergic effects become prominent with peripheral vasoconstriction.

Experience with the use of dopamine in pediatric patients suggests that it is effective in increasing blood pressure in neonates, infants, and children. The precise dosages at which the desired hemodynamic effects are maximized are not known. The effects of low dosages of dopamine on blood pressure, heart rate, and renal function were studied in 18 hypotensive, preterm infants.[71] The blood pressure and diuretic effects were observed at 2, 4, and 8 μg/kg/min. Elevations in heart rate were seen only at 8 μg/kg/min. Further work is needed to better characterize the pharmacokinetics and pharmacodynamics of dopamine in children, especially in newborns.

Dobutamine

Dobutamine, a synthetic catecholamine, has predominantly β-adrenergic effects with minimal α-adrenergic effects. The hemodynamic effect of dobutamine in infants and children with shock has been studied.[72] Dobutamine infusion significantly increased cardiac index, stroke index, and pulmonary capillary wedge pressure, and it decreased SVR. The drug appears more efficacious in treating cardiogenic shock than septic shock. The advantage of dobutamine over isoproterenol is its lesser chronotropic effect and its tendency to maintain systemic pressure. The advantage over dopamine is dobutamine's lesser peripheral vasoconstrictor effect. The usual range of dosages for dobutamine is 1–10 μg/kg/min. The combination of dopamine and dobutamine has been increasingly used; however, little information regarding their combined advantages or effectiveness in the neonate and infant has been published.

Milrinone

Milrinone, a phosphodiesterase inhibitor, is a potent positive inotrope and vasodilator (hence, also known as an ino-dilator) that has been shown to improve cardiac function in infants and children.[73–75] The proposed action is due, in part, to an increase in intracellular cyclic adenosine monophosphate and calcium transport secondary to inhibition of cardiac phosphodiesterase. This effect is independent of β-agonist stimulation and, in fact, may act synergistically with the β agonist to improve cardiac performance. Milrinone increases cardiac index and oxygen delivery without affecting heart rate, blood pressure, or pulmonary wedge pressure. Milrinone is administered as a 75 μg/kg bolus followed by infusion of 0.75–1.0 g/kg/min.

DISTRIBUTIVE SHOCK

Distributive shock is caused by derangements in vascular tone from endothelial damage that lead to end-organ hypotension and is seen in the following clinical situations: (1) septic shock, (2) SIRS, (3) anaphylaxis, and (4) spinal cord trauma. Septic shock in the pediatric patient is discussed in further detail.

SEPTIC SHOCK

Afterload represents the force against which the left ventricle must contract to eject blood. It is related to SVR and myocardial wall stress. SVR is defined as the systemic mean arterial blood pressure minus right arterial pressure divided by cardiac output. Cardiac contractility is affected by SVR and afterload. In general, increases in afterload reduce cardiac contractility, and decreases in afterload increase cardiac contractility.

Septic shock is a distributive form of shock that differs from other forms of shock. Cardiogenic and hypovolemic shock lead to increased SVR and decreased cardiac output. Septic shock results from a severe decrease in SVR and a generalized maldistribution of blood and leads to a hyperdynamic state.[76] The pathophysiology of septic shock begins with a nidus of infection. Organisms may invade the blood stream, or they may proliferate at the infected site and release various mediators into the blood stream. Substances produced by microorganisms, such as lipopolysaccharide, endotoxin, exotoxin, lipid moieties, and other products can induce septic shock by stimulating host cells to release numerous cytokines, chemokines, leukotrienes, and endorphins.

Endotoxin is a lipopolysaccharide found in the outer membrane of Gram-negative bacteria. Functionally, the molecule is divided into three parts: (1) the highly variable O-specific polysaccharide side chain (conveys serotypic specificity to bacteria and can activate the alternate pathway of complement); (2) the R-core region (less variable among different Gram-negative bacteria; antibodies to this region could be cross protective); and (3) lipid-A (responsible for most of the toxicity of endotoxin). Endotoxin stimulates tumor necrosis factor (TNF) and can directly activate the classic complement pathway in the absence of antibody. Endotoxin has been implicated as an important factor in the pathogenesis of human septic shock and Gram-negative sepsis.[77] Therapy has focused on developing antibodies to endotoxin to treat septic shock. Antibodies to endotoxin have been used in clinical trials of sepsis with variable results.[78–80]

Cytokines, especially TNF, play a dominant role in the host's response. Endotoxin and exotoxin both induce TNF release in vivo and produce many other toxic effects via this endogenous mediator.[81–83] TNF is released primarily from monocytes and macrophages. It is also released from natural killer cells, mast cells, and some activated T-lymphocytes. Antibodies against TNF protect animals from exotoxin and bacterial challenge.[84,85] Other stimuli for its release include viruses, fungi, parasites, and interleukin-1

(IL-1). In sepsis, the effects of TNF release may include cardiac dysfunction, disseminated intravascular coagulation, and cardiovascular collapse. TNF release also causes the release of granulocyte–macrophage colony-stimulating factor (GM-CSF), interferon-α, and IL-1.

IL-1 is produced primarily by macrophages and monocytes. IL-1, previously known as the endogenous pyrogen, plays a central role in stimulating a variety of host responses, including fever production, lymphocyte activation, and endothelial cell stimulation, to produce procoagulant activity and to increase adhesiveness. IL-1 also causes the induction of the inhibitor of tissue plasminogen activator and the production of GM-CSF. These effects are balanced by the release of platelet-activating factor and arachidonic metabolites.

IL-2, also known as *T-cell growth factor*, is produced by activated T-lymphocytes and strengthens the immune response by stimulating cell proliferation. Its clinically apparent side effects include capillary leak syndrome, tachycardia, hypotension, increased cardiac index, decreased SVR, and decreased left ventricular ejection fraction.[86,87]

Studies in dogs have suggested that in immature animals, septic shock is more lethal and has different mechanisms of tissue injury.[88] These include more dramatic aberrations in blood pressure (more constant decline), heart rate (progressive, persistent tachycardia), blood sugar level (severe, progressive hypoglycemia), acid–base status (severe acidosis), and oxygenation (severe hypoxemia). These changes are significantly different from those seen in the adult animals that also experience an improved survival of almost 600% (18.5 vs 3.1 hours) compared with the immature animal.

The neonate's host defense can usually respond successfully to ordinary microbial challenge. However, defense against major challenges appears limited, which provides an explanation for the high mortality rate with major neonatal sepsis. As in adults, the immune system consists of four major components: cell-mediated immunity (T-cells), complement system, antibody-mediated immunity (B-cells), and macrophage–neutrophil phagocytic system. The two most important deficits in newborn host defenses that seem to increase the risk of bacterial sepsis are the quantitative and qualitative changes in the phagocytic system and the defects in antibody-mediated immunity.

The proliferative rate of the granulocyte–macrophage precursor has been reported to be at near-maximal capacity in the neonate. However, the neutrophil storage pool is markedly reduced in the newborn compared with the adult. After bacterial challenge, newborns fail to increase stem cell proliferation and deplete their already reduced neutrophil storage pool. Numerous in vitro abnormalities have been demonstrated in neonatal polymorphonuclear neutrophils, especially in times of stress or infection.[89] These abnormalities include decreased deformability, chemotaxis, phagocytosis, C3b receptor expression, adherence, bacterial killing, and depressed oxidative metabolism. Chemotaxis is impaired in neonatal neutrophils in response to various bacterial organisms and antigen–antibody complexes.[90] Granulocytes are activated by their interaction with endothelial cells followed by entry into secondary lymphoid issues via the endothelial venules. Initial adhesion of granulocytes is dependent on their expression of L-selectin, a cell adhesion molecule expressed on the granulocyte cell surface. Evaluation of cord blood has demonstrated a significantly lower expression of L-selectin on granulocyte surfaces when compared with older newborn (5 days old) and adult samples, indicating a depressed level of interaction with vascular endothelial cells at the initial stage of adhesion.[91] Although phagocytosis has additionally been demonstrated to be abnormal in neonatal phagocytes, it appears that this phenomenon is most likely secondary to decreased opsonic activity rather than an intrinsic defect of the neonatal polymorphonuclear neutrophils.[92,93] Currently, there is inconclusive evidence to support or refute the routine use of granulocyte transfusions in the prevention or treatment of sepsis in the neonate.[94]

Preterm and term newborns have poor responses to various antigenic stimuli, reduced gamma globulin levels at birth, and reduced maternal immunoglobulin supply from placental transport. Almost 33% of infants with a birth weight less than 1500 g develop substantial hypogammaglobulinemia.[95] IgA and IgM levels are also low due to the inability of these two immunoglobulins to cross the placenta. Thus, neonates are usually more susceptible to pyogenic bacterial infections because most of the antibodies that opsonize pyogenic bacterial capsular antigens are IgG and IgM. In addition, neonates do not produce type-specific antibodies because of defects in the differentiation of B-lymphocytes into immunoglobulin-secreting plasma cells and in T-lymphocyte-mediated facilitation of antibody synthesis. In the term infant, total hemolytic complement activity, which measures the classic complement pathway, constitutes approximately 50% of adult activity.[96] The activity of the alternative complement pathway, secondary to lowered levels of factor B, is also decreased in the neonate.[97] Fibronectin, a plasma protein that promotes reticuloendothelial clearance of invading microorganisms, is deficient in neonatal cord plasma.[98]

The use of intravenous immunoglobulins (IVIGs) for the prophylaxis and treatment of sepsis in the newborn, especially the preterm, low birth weight infant, has been studied in numerous trials with varied outcomes. In one study, a group of infants weighing 1500 g was treated with 500 mg/kg of IVIG each week for 4 weeks and compared with infants who were not treated with immunoglobulin.[99] The death rate was 16% in the IVIG-treated group compared with 32% in the untreated control group. Another analysis examined the role of IVIG to prevent and treat neonatal sepsis.[100] A significant (but only marginal) benefit was noted from prophylactic use of IVIG to prevent sepsis in low birth weight premature infants. However, using IVIG to treat neonatal sepsis produced a greater than 6% decrease in the mortality rate. A review of 19 randomized control trials found a 3% decrease in the incidence of neonatal sepsis in preterm infants without a significant difference in all-cause and infection-related mortality when prophylactic IVIG was administered.[101] Based on the marginal reduction of neonatal sepsis without a reduction in mortality, routine use of prophylactic IVIG cannot be recommended.

Colony-stimulating factors (CSFs) are a family of glycoproteins that stimulate proliferation and differentiation of hematopoietic cells of various lineages. GM-CSF and granulocyte CSF (G-CSF) have similar physiologic actions. Both

stimulate the proliferation of bone marrow myeloid progenitor cells, induce the release of bone marrow neutrophil storage pools, and enhance mature neutrophil effect or function.[100–102] Preliminary studies of GM-CSF in neonatal animals demonstrate enhancement of neutrophil oxidative metabolism as well as priming of neonatal neutrophils for enhanced chemotaxis and bacterial killing. Both GM-CSF and G-CSF induce peripheral neutrophilia within 2–6 hours of intraperitoneal administration. This enhanced affinity for neutrophils returns to normal baseline level by 24 hours.[103] Studies have confirmed the efficacy and safety of G-CSF therapy for neonatal sepsis and neutropenia.[104] Other investigations have demonstrated no long-term adverse hematologic, immunologic, or developmental effects from G-CSF therapy in the septic neonate. Prolonged prophylactic treatment in the very low birth weight neonate with recombinant GM-CSF has been shown to be well tolerated and to result in a significant decrease in the rate of nosocomial infections.[105,106]

Unique to the newborn in septic shock is the persistence of fetal circulation and resultant pulmonary hypertension.[107] In fact, the rapid administration of fluid can further exacerbate this problem by causing left-to-right shunting through a patent ductus arteriosus (PDA) and subsequent congestive heart failure from ventricular overload. Infants in septic shock with a new heart murmur should undergo a cardiac echocardiogram. If present, a PDA may warrant treatment with indomethacin (prostaglandin inhibitor) or surgical ligation to achieve closure, depending on the clinical picture.

The critical care of a neonate/infant in septic shock can be extremely challenging. Septic shock has a distinctive clinical presentation and is characterized by an early compensated stage where one can see a decreased SVR, an increase in cardiac output, tachycardia, warm extremities, and an adequate urine output. Later in the clinical presentation, septic shock is characterized by an uncompensated phase in which one will see a decrease in intravascular volume, myocardial depression, high vascular resistance, and a decreasing cardiac output.[108] Management of these patients is based on the principles of source control, antibiotics (broad-spectrum, institutionally based when possible and including antifungal agents as warranted), and supportive care.

Patients with severe septic shock often do not respond to conventional forms of volume loading and cardiovascular supportive medications. The administration of arginine vasopressin has been shown to decrease mortality in adult patients with recalcitrant septic shock.[109,110] Vasopressin (see Table 1.6), also known as antidiuretic hormone (ADH), is made in the posterior pituitary and plays a primary role in water regulation by the kidneys. In septic shock, vasopressin has profound effects on increasing blood pressure in intravascular depleted states. Sparked initially by a randomized, double-blinded, placebo-controlled study in adults that demonstrated a beneficial effect of vasopressin in recalcitrant septic shock, its utilization in the pediatric population has become common.[111,112]

While a detailed discussion is beyond the scope of this chapter (please refer to Chapter 6), current trends suggest that ECMO may serve as rescue therapy in select patients with profound sepsis and cardiopulmonary failure refractory to other measures (reported ELSO database newborn survival 80%, older children 50%).[112,113]

Given the difficult nature of caring for septic patients, extensive investigation has been launched in an attempt to identify patients at risk.[114–116] Early serum markers such as C-reactive protein, IL-6, and procalcitonin carry promise but warrant further validation.

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2 Nutritional Support for the Pediatric Patient

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Despite advances in the field of nutritional support, malnutrition among hospitalized pediatric patients, especially those with a protracted clinical course, remains prevalent worldwide and is associated with worse outcomes.[1–5] Moreover, it has been well established that preoperative malnutrition is associated with higher postoperative mortality.[6,7] Optimal nutritional therapy requires a careful assessment of the child's energy needs and the provision of macronutrients and micronutrients via the most suitable feeding route. The profound and stereotypic metabolic response to injury places unique demands on the hospitalized child. Standard equations available for estimating energy needs have proven to be unreliable in this population.[8,9] In addition, children with critical illness have a marked net protein catabolism and often lack adequate nutritional support.[10] Ultimately, an individualized nutritional regimen should be tailored for each child and reviewed regularly during the course of illness. An understanding of the metabolic events that accompany illness and surgery in a child is the first step in implementing appropriate nutritional support. Although this chapter focuses on the short-term outcomes and management related to nutritional status in the acutely ill child, it is important to be aware of the potential long-term effects of suboptimal nutrition in children and infants, particularly pertaining to metabolic consequences and neurodevelopment.[11–13]

The Metabolic Response to Stress

The metabolic response to illness due to stressors such as trauma, surgery, or inflammation has been well described, and the magnitude of the response varies according to illness severity. Cuthbertson was the first investigator to realize the primary role that whole-body protein catabolism plays in the systemic response to injury.[14] Based on his work, the metabolic stress response has been conceptually divided into two phases. The initial, brief "ebb phase" is characterized by decreased enzymatic activity, reduced oxygen consumption, low cardiac put, and core temperature that may be subnormal. This is followed by the hypermetabolic "flow phase" characterized by increased cardiac output, oxygen consumption, and glucose production. During this phase, fat and protein mobilization is manifested by increased urinary nitrogen excretion and weight loss. This catabolic phase is mediated by a surge in cytokines and the characteristic endocrine response to trauma or surgery that results in an increased availability of substrates essential for healing and glucose production.

Neonates and children share similar qualitative metabolic responses to illness as adults, albeit with significant quantitative differences. The metabolic stress response is beneficial in the short term, but the consequences of sustained catabolism are significant because the child has limited tissue stores and substantial nutrient requirements for growth. Thus, the prompt institution of nutritional support is a priority in sick neonates and children. The goal of nutrition in this setting is to augment the short-term benefits of the metabolic response to injury while minimizing negative consequences of persistent catabolism. In general, the metabolic stress response is characterized by an increase in net muscle protein degradation and the enhanced movement of free amino acids through the circulation (Fig. 2.1). These amino acids serve as the building blocks for the rapid synthesis of proteins that act as mediators for the inflammatory response and structural components for tissue repair. The remaining amino acids not used in this way are channeled through the liver, where their carbon skeletons are utilized to create glucose through gluconeogenesis. The provision of additional dietary protein may slow the rate of net protein loss, but it does not eliminate the overall negative protein balance associated with injury.[15]

Carbohydrate and lipid turnover are also increased severalfold during the metabolic response. Although these metabolic alterations would be expected to increase overall energy requirements, data show that such an increase is quantitatively variable, modest, and evanescent. Overall, the energy needs of the critically ill or injured child are governed by the severity and persistence of the underlying illness or injury. Accurate assessment of energy requirements in individual patients allows optimal caloric supplementation and avoids the deleterious effects of both underfeeding and overfeeding.

Children with critical illness demonstrate a unique hormonal and cytokine profile.[16] A transient decrease in insulin levels is followed by a persistent elevation, the anabolic effects of which are overcome by increased levels of catabolic hormones (glucagon, cortisol, catecholamines). This overall catabolic state is marked by increases in specific inflammatory cytokines (interleukin [IL]-6, tumor necrosis factor [TNF]-α). Novel ways to manipulate these hormonal and cytokine alterations with an aim to minimize the deleterious consequences induced by the stress response are a focus of research.[17,18]

Body Composition and Nutrient Reserves

The body composition of the young child contrasts with that of the adult in several ways that significantly affect

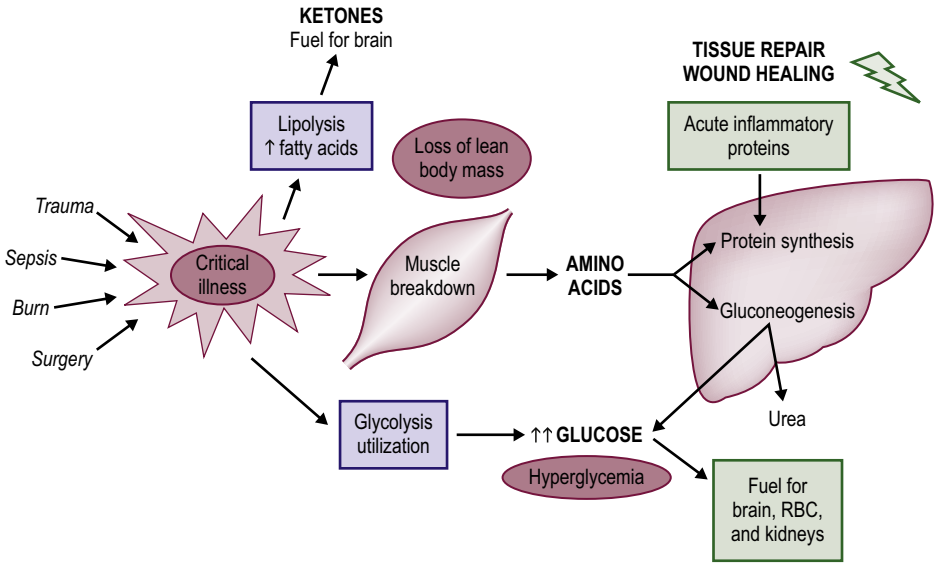

Fig. 2.1 The metabolic changes associated with the pediatric stress response to critical illness and injury. In general, net protein catabolism predominates and amino acids are transported from muscle stores to the liver, where they are converted to inflammatory proteins and glucose through the process of gluconeogenesis. *RBC,* Red Blood Cells.

Table 2.1 Body Composition of Neonates, Children, and Adults as a Percentage of Total Body Weight

Age	Protein (%)	Fat (%)	Carbohydrate (%)
Neonates	11	14	0.4
Children (age 10 yr)	15	17	0.4
Adults	18	19	0.4

Table 2.2 Estimated Requirements for Energy and Protein in Healthy Humans of Different Age Groups

Age	Protein (g/kg/day)	Energy (kcal/kg/day)
Infants (age 0–6 mo)	1.5–2.2	105–120
Children (age 10 yr)	0.8–1.0	60–70
Adults	0.7–0.8	35–40

nutritional requirements. Table 2.1 lists the macronutrient stores of the neonate, child, and adult as a percentage of total body weight.[19,20] Carbohydrate stores are limited in all age groups and provide only a short-term supply of glucose. Despite this fact, neonates have a high demand for glucose and have shown elevated rates of glucose turnover compared with those of the adult.[21] This is thought to be related to the neonate's increased ratio of brain-to-body mass because glucose is the primary energy source for the central nervous system. Neonatal glycogen stores are even more limited in the early postpartum period, especially in the preterm infant.[22] Short periods of fasting can predispose the newborn to hypoglycemia. Therefore, when infants are burdened with illness or injury, they must rapidly turn to the breakdown of protein stores to generate glucose through the process of gluconeogenesis. In premature infants, gluconeogenesis is sustained despite provision of parenteral nutrition (PN) with glucose infusion rates higher than endogenous glucose production rate.[23]

Lipid reserves are low in the neonate, gradually increasing with age. Premature infants have the lowest proportion of lipid stores because the majority of polyunsaturated fatty acids accumulate in the third trimester.[24] This renders lipid less available as a potential fuel source in the young child. The most dramatic difference between adult and pediatric patients is in the relative quantity of stored protein. The protein reserve per kilogram of ideal body weight in the adult is nearly twofold that of the neonate. Thus, infants cannot afford to lose significant amounts of protein during the course of a protracted illness or injury. An important feature of the metabolic stress response, unlike in starvation, is that the provision of dietary glucose does not halt gluconeogenesis. Consequently, the catabolism of muscle protein to produce glucose continues unabated.[25] Neonates and children also share much higher baseline energy requirements than adults. In addition, among preterm infants with low birth weight, the birth weight inversely correlates with resting energy expenditure (REE).[26] Clearly, the child's need for rapid growth and development is a large component of this increase in energy requirement. Moreover, increased heat loss via the relatively large body surface area of the young child and immature thermoregulation in preterm infants further contribute to elevations in energy expenditure.

The basic requirements for protein and energy in the healthy neonate, child, and adult, based on recommendations by the National Academy of Sciences, are listed in Table 2.2.[27,28] As illustrated, the recommended protein needs for the infant are two to three times those of the adult. In premature infants, a minimum protein allotment of 2.8 g/kg/day is required to maintain in utero growth rates.[29] The increased metabolic demand and limited nutrient reserves of the infant mandates early nutritional support in times of injury and critical illness to avoid negative nutritional consequences.

An accurate assessment of body composition is necessary for planning nutritional intake, monitoring dynamic

changes in the body compartments (such as the loss of lean body mass), and assessing the adequacy of nutritional supportive regimens during critical illness. Ongoing loss of lean body mass is an indicator of inadequate dietary supplementation and may have clinical implications in the hospitalized child. However, current methods of body composition analysis (e.g., anthropometry, weight and biochemical parameters) are either impractical for clinical use or inaccurate in a subgroup of hospitalized children with critical illness.[30] One of the principal problems in critically ill children is the presence of capillary leak, manifesting as edema and large fluid shifts. These make anthropometric measurements invalid, and other bedside techniques have not been adequately validated.

Energy Expenditure During Illness

For children with illness or undergoing operative intervention, knowledge of energy requirements is important for the design of appropriate nutritional strategies. Dietary regimens that both underestimate and overestimate energy needs are associated with negative consequences. Owing to the high degree of individual variability in energy expenditure, particularly in the most critically ill patients, the actual measurement of REE is recommended.

The components of total energy expenditure (TEE) for a child in order of magnitude are REE, energy expended during physical activity (PA), and diet-induced thermogenesis (DIT). The sum of these components determines the energy requirement for an individual. In general, REE rates decline with age from infancy to young adulthood, at which time the rate becomes stable. In children with critical illness, the remaining factors in the determination of total energy requirement are of reduced significance because PA is low and DIT may not be significant.

REE can be measured using direct or indirect methods. The direct calorimetric method measures the heat released by a subject at rest and is based on the principle that all energy is eventually converted to heat. In practice, the patient is placed in a thermally isolated chamber, and the heat dissipated is measured for a given period.[31] This method is the true gold standard for measured energy expenditure. Direct calorimetry is not practical for most hospitalized children, and REE is often estimated using standard equations. Unfortunately, REE estimates using standardized World Health Organization (WHO) predictive equations are unreliable, particularly in critically ill children.[8,9]

REE estimation is difficult in critically ill or postoperative children. Their energy requirements show individual variation and depend on severity of injury, sedation, and environmental factors. For instance, a mechanically ventilated child with severe traumatic brain injury who is being treated with sedation and neuromuscular blockade would have a much lower energy expenditure than a severely burned child in a nonthermoneutral environment. Infants with congenital diaphragmatic hernia on extracorporeal membrane oxygenation (ECMO) support have been shown to have energy expenditures of approximately 90 kcal/kg/day.[32] Following extubation, the same patients may have energy requirements as high as 125 kcal/kg/day to achieve desired growth velocity at hospital discharge.[33] Although stress factors ranging from 1.0 to 2.7 have been applied to correct for these variations, calculated standardized energy expenditure equations have not been satisfactorily validated in critically ill children.[34–38] The most recent guidelines for nutrition support in critically ill children, published jointly by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society of Critical Care Medicine (SCCM), recommend that if estimating equations are used, the Schofield, WHO, or United Nations University equations may be applied without the addition of stress factors.[39]

Indirect calorimetry measures VO_2 (the volume of oxygen consumed) and VCO_2 (the volume of CO_2 produced) and uses a correlation factor based on urinary nitrogen excretion to calculate the overall rate of energy production.[40] The measurement of energy needs is "indirect" because it does not use direct temperature changes to determine energy needs. Indirect calorimetry provides a measurement of the overall respiratory quotient (RQ), defined as the ratio of CO_2 produced to O_2 consumed (VCO_2/ VO_2) for a given patient. Oxidation of carbohydrate yields an RQ of 1.0, whereas fatty acid oxidation gives an RQ of 0.7. However, the role of the RQ as a marker of substrate use and an indicator of underfeeding or overfeeding is limited. The body's ability to metabolize substrate may be impaired during illness, making assumptions about RQ values and substrate oxidation invalid.

Although RQ is not a sensitive marker for adequacy of feeding in individual cases, RQ values greater than 1.0 can be associated with lipogenesis secondary to overfeeding.[41] However, numerous factors, related and unrelated to feeding, can alter the value of a measured RQ in critically ill patients, for example, hyperventilation, acidosis, effects of cardiotonic agents and neuromuscular blocking, and an individual response to a given substrate load, injury, or disease. Furthermore, in the setting of wide diurnal and day-to-day variability of REE in critically ill individuals, the extrapolation of short-term calorimetric REE measurements to 24-hour REE may introduce errors. The use of steady-state measurements may decrease these errors. Steady state is defined by change in VO_2 and VCO_2 of <10% over a period of 5 consecutive minutes. The values for the mean REE from this steady-state period may be used as an accurate representation of the 24-hour TEE in patients with low levels of PA.[42] In a patient who fails to achieve steady state and is metabolically unstable, prolonged testing is required (minimum of 60 minutes) and 24-hour indirect calorimetry should be considered.

Indirect calorimetry is not accurate in the setting of air leaks around the endotracheal tube, in the ventilator circuit or through a chest tube, or in patients on ECMO. A high inspired oxygen fraction (FiO_2 >0.6) will also affect indirect calorimetry. Indirect calorimetry is difficult to use in babies on ECMO because a large proportion of the patient's oxygenation and ventilation is performed through the membrane oxygenator. The use of indirect calorimetry for assessment and monitoring of nutrition intake requires attention to its limitations and expertise in the interpretation, as well as specialized equipment and personnel. Nonetheless, its application in children at high risk for underfeeding and overfeeding can be helpful.[43,44]

Nonradioactive stable isotope techniques have been used to measure REE in the pediatric patient. Stable isotope technology has been available for many years and has been crucial in the study of many metabolic pathways. It was first applied for energy expenditure measurement in humans in 1982.[45] The highly sensitive techniques of quantifying stable isotopes minimize measurement error, but the high cost of the isotopes and specialized equipment has led to limited clinical use.[46]

In general, any increase in energy expenditure during illness or after an operation is variable, and studies suggest that the increase is far less than originally hypothesized. Newborns undergoing major surgery have only a transient 20% increase in energy expenditure that returns to baseline values within 12 hours postoperatively, provided no major complications develop.[47] In one study, REE measurements immediately postoperatively in children with single-ventricle heart defects who underwent a Fontan procedure found a low prevalence of hypermetabolism.[48] In another study, stable extubated neonates, 5 days after operation, were shown to have REE comparable to normal infants.[49] Effective anesthetic and analgesic management may play a significant role in muting the stress response of the surgical neonate.[50] A retrospective stratification of surgical infants into low- and high-stress cohorts based on the severity of underlying illness found that infants under high stress experience moderate short-term elevations in energy expenditure after operation, whereas infants under low stress do not manifest any increase in energy expenditures during the course of illness.[51] Finally, by using stable isotopic methods, it has been found that the mean energy expenditures of critically ill neonates on ECMO are nearly identical to age- and diet-matched stable surgical neonates.[52]

These studies suggest that critically ill neonates have only a small and usually short-term increase in energy expenditure. Although children have increased energy requirements from the increased metabolic turnover during illness, their overall caloric needs may be lower than previously thought due to possible halted or slowed growth and the use of sedation and muscle paralysis. This could result in overfeeding when energy intake is based on presumed or estimated energy expenditure with stress factors. On the other hand, unrecognized hypermetabolism in select individuals results in underfeeding with negative nutritional consequences. The variability in energy requirements may result in cumulative energy imbalances in the intensive care unit (ICU) over time.[38,53]

For practical purposes, the recommended dietary caloric intake for healthy children may represent a reasonable starting point for the upper limit of caloric allotment for hospitalized children.[27,28] However, as discussed earlier, energy requirement estimates in select groups of patients remain variable and possibly overestimated, mandating an accurate estimation using measured energy expenditure where available. Regular anthropometric measurements plotted on a growth chart to assess the adequacy of caloric provision will allow relatively prompt detection of underfeeding or overfeeding in most cases. However, some critically ill children may be too sick for regular weights or have changes in body water that make anthropometric measurements unreliable. The Tight Calorie Control Study (TICACOS) showed that nutritional support guided by repeated indirect calorimetry measurements in mechanically ventilated adults resulted in more frequent achievement of energy goals with higher protein delivered and a trend to lower mortality.[54] A pediatric trial of PN titrated to measured REE in children after hematopoietic stem cell transplantation did not lead to differences in body composition.[55] Further study into the potential benefit of nutritional delivery guided by serial measures of energy expenditure in children is warranted. VCO_2-based REE prediction, which relies on more widely available equipment for bedside monitoring, may make continuous metabolic assessment in mechanically ventilated patients more feasible.[56]

Macronutrient Intake

PROTEIN METABOLISM AND REQUIREMENT DURING ILLNESS

Amino acids are the key building blocks required for growth and tissue repair. The majority (98%) are found in existing proteins, and the remainder reside in the free amino acid pool. Proteins are continually degraded into their constituent amino acids and resynthesized through the process of protein turnover. The reutilization of amino acids released by protein breakdown is extensive. Synthesis of proteins from the recycling of amino acids is more than two times greater than from dietary protein intake. An advantage of high protein turnover is that a continuous flow of amino acids is available for the synthesis of new proteins. This allows the body tremendous flexibility in meeting ever-changing physiologic needs. However, the process of protein turnover requires the input of energy to power both protein degradation and synthesis. At baseline, infants are known to have higher rates of protein turnover than adults. Healthy newborns have a protein-turnover rate of 6–12 g/kg/day compared with 3.5 g/kg/day in adults.[57] Even greater rates of protein turnover have been measured in premature infants and those with low birth weight.[58] For example, it has been demonstrated that infants with extremely low birth weight receiving no dietary protein can lose in excess of 1.2 g/kg/day of endogenous protein.[59] At the same time, infants must maintain a positive protein balance to attain normal growth and development, whereas the healthy adult can subsist with a neutral protein balance.

In the metabolically stressed patient, such as the child with severe burn injury, sepsis, or major surgery, protein turnover is increased up to twofold compared with that in normal children, which has been shown to correlate with the duration of the critical illness and severity of injury.[60,61] This process redistributes amino acids from skeletal muscle to the liver, wound, and tissues taking part in the inflammatory response. The factors required for the inflammatory response (acutely needed enzymes, serum proteins, and glucose) are thereby synthesized from degraded body protein stores. The well-established increase in hepatically derived acute phase proteins (including C-reactive protein, fibrinogen, transferrin, and α-1-acid glycoprotein), along with the concomitant decrease in transport proteins (albumin and retinol-binding protein), is evidence of this protein redistribution. As substrate turnover is increased during