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RESPIRATORY PROBLEMS IN TERM INFANTS

Unlike the typical respiratory problems of prematurely delivered newborns that result from inadequate surfactant production, the mechanisms of respiratory problems in term infants (≥ 37 weeks of gestation) are associated with inadequate pulmonary perfusion (e.g., persistent pulmonary hypertension of the newborn) as well as surfactant deficiency due to both inadequate production (e.g., in the late preterm infant) and inactivation [e.g., meconium aspiration syndrome (MAS), congenital pneumonia]. Finally, both spontaneous airleaks and congenital abnormalities of airway, pulmonary parenchyma, or pulmonary vascular development (e.g., congenital diaphragmatic hernia, alveolar-capillary dysplasia) present as respiratory distress in the term newborn. Although term infants are less likely to suffer from respiratory problems than preterm infants, their risk for respiratory distress has been estimated at 0.6% in one large prospective study (1) and their risk for severe respiratory distress that requires mechanical ventilation at $\sim 0.2\%$ (2).

MAS

Although most infants delivered after exposure to meconium-stained amniotic fluid will exhibit no symptoms, a subgroup may develop severe respiratory failure. Understanding the pathophysiology of this subgroup has been enhanced by understanding fetal lung physiology. Net fluid flow in the fetal lung results from an egress of fluid from pulmonary epithelial cells into future airspaces and airways. The flow of fetal lung fluid across the glottis into the amniotic cavity keeps contaminants in the amniotic fluid (e.g., meconium, squamous cells, and blood) downstream from pulmonary epithelial cells in utero. Aspiration of these agents may occur if the fetus is "gasping," a fetal behavior associated with severe hypoxia or ischemia. Exposure of the pulmonary epithelium to meconium leads to evidence of significant injury with elaboration of cytokines associated with inflammation, altered surfactant metabolism, and histologic evidence of airspace overdistention. These pathophysiologic mechanisms help explain the ventilatory problems associated with MAS and increased risk of airleaks (3). The associated hypoxia and acidosis, particularly if preceded by prolonged intrauterine distress with increase in the thickness of the muscularis layer in the smaller pulmonary branch vessels (4), contribute to failure to achieve normal pulmonary vasorelaxation and to worsening hypoxia and hypercarbia in a cyclic fashion. Thus, both severe pulmonary parenchymal injury and pulmonary hypertension contribute to the presentation and must be treated.

MAS occurs in 0.6% to 0.7% of all newborn infants with any respiratory symptoms and in 0.04% of newborn infants who

require mechanical ventilation (2,5,6). Although risk for other common respiratory problems [e.g., transient tachypnea of the newborn (TTN) or respiratory distress syndrome (RDS)] decreases with advancing gestational age, risk for MAS increases with advancing gestational age. Approximately one-third of symptomatic infants will require mechanical ventilation, and despite surfactant replacement and availability of high-frequency oscillatory ventilation (HFOV) and nitric oxide (NO) treatment, mortality is reported in 2.5% of infants who require ventilatory support (down from 12% before widespread adoption of HFOV and NO).

Over the last decade, approaches to intrapartum and immediate postpartum prevention of MAS have moved away from attempts to evacuate the upper airway of meconium by obstetricians at delivery of the head and by pediatricians after the delivery is complete. These interventions were found to be helpful in small historical control studies in the 1970s. However, larger randomized controlled trials reported in the 1990s failed to demonstrate any improvement in outcomes and raised concerns about associated iatrogenic injury to the upper airway in some infants. The official 2005 recommendation of the American Heart Association and the American Academy of Pediatrics makes clear that in the setting of infants born with thick meconium staining, the priority is to reserve intubation only for the infants who are most depressed at birth and not routinely to aspirate the mouth and nose (7). Similarly, although initial randomized studies of amnioinfusions for meconium-stained amniotic fluid found a beneficial effect on neonatal respiratory outcomes without increased maternal morbidity, a large multicenter randomized study (8) reported no routine benefit from amnioinfusion. The American College of Obstetrics and Gynecology revised its practice guideline to indicate that although amnioinfusion remains an appropriate intervention for treatment of fetal distress (with or without meconium-stained amniotic fluid) evaluated by heart rate monitoring, it is not effective for reduction of risk of MAS (9,10).

TTN

First described by Mary Ellen Avery in 1966 (11), this self-limited (hours to a few days) condition is characterized by presentation within the first few hours of life with tachypnea, a radiographic picture of increased perihilar pulmonary vascular markings, fluid in the pulmonary lobar fissure, and increased lung volumes. Both the severity and duration of symptoms vary but are generally less intense than those seen in respiratory disorders like MAS or congenital pneumonia. As noted earlier, net fetal lung liquid production leads to egress of fluid into the amniotic cavity. Just prior to birth, this

chloride-rich fluid production by the lung epithelium switches to fluid resorption driven by amiloride-sensitive sodium channels. The reversal of chloride and water transport leads to a decrease in total lung water before delivery. This process is dependent on long-term, developmentally regulated changes in the expression of sodium channels and their adrenoceptor sensitivity, more acute changes in ambient catecholamine levels associated with labor and delivery, and transition to the relatively oxygen-rich postnatal environment (12). Failure of this process of adaptation to the extrauterine environment in the absence of infection, surfactant deficiency or inactivation, or relevant birth defects is believed to cause the symptom complex known as TTN.

In keeping with this proposed mechanism, the risk factors associated with higher risk of TTN are those that interfere with normal adaptation from placenta-dependent gas exchange in utero to lung-dependent gas exchange in the extrauterine environment. Shorter gestation may lead to lower levels of expression of critical components of the sodium channel assembly, its catecholamine regulators, and surfactant (the risk of developing TTN increases with decreasing gestational age). Additionally, absent or shortened labor (e.g., in the settings of elective cesarean section without labor or of rapid second phase of labor) provides less time for alveolar fluid resorption and is associated with the development of TTN. Finally, disease risk may be increased by genetic factors, for example, polymorphisms in β adrenoceptor gene (13). Recent studies have reinforced the association of TTN with both earlier gestational age and cesarean delivery mode (14–16).

RESPIRATORY DISTRESS IN PRETERM INFANTS

Despite advances in the care of infants born prematurely, prematurity (delivery at <37 weeks of gestation) remains one of the leading causes of neonatal death (17). The incidence of RDS, a major complication of prematurity, is directly related to lower gestational age at birth. The incidence of RDS in infants born at 25 weeks of gestation approaches 100%. At 27 weeks of gestation, the incidence decreases to approximately 85%, at 30 weeks of gestation to 55%, at 32 weeks of gestation to 30%, and by 35 weeks of gestation to 10% (18). In addition to prematurity, other factors that predispose to RDS include male gender, European ancestry, maternal diabetes, perinatal hypoxemia, hypothermia, multifetal pregnancy, and cesarean delivery (19). An increase in the rate of preterm deliveries over the last several years, attributable primarily to infants delivered between 34 and 37 weeks of gestation (late preterm infants) (See section below entitled “Late Preterm Neonates.”), has contributed significantly to the burden of newborn respiratory distress (20).

In 1959, Mary Ellen Avery and Jere Mead described the relationship between preterm birth, lung surface tension, and RDS (21). Since that time, understanding the biology of pulmonary surfactant and its role in preterm respiratory distress has been one of the triumphs of newborn medicine. This understanding has led to the use of exogenous surfactant replacement as a primary treatment for preterm RDS. Available surfactant preparations include bovine- or porcine-derived products and synthetic surfactant preparations that are administered to preterm infants via endotracheal tube. Multiple studies have demonstrated the efficacy of exogenous

surfactant in reducing newborn mortality and airleaks, especially when given as multiple doses early after birth in a prophylactic, as opposed to rescue, manner (22,23). Although a consistent reduction in the development of chronic lung disease (bronchopulmonary dysplasia) in preterm infants treated with surfactant has not been demonstrated, there is evidence that the severity of chronic lung disease has decreased in the era of surfactant therapy (24). Combined management strategies, for example, surfactant treatment and early extubation to continuous positive airway pressure (CPAP), show promise in decreasing not only the severity but the incidence of chronic lung disease in preterm infants with RDS as well (25,26).

In the late 1960s, Graham Liggins made the seminal observation that lambs exposed in utero to corticosteroids and delivered prematurely had less respiratory distress, more mature appearing lungs, and decreased mortality (27). By 1972, the first human trial demonstrating the efficacy of antenatal corticosteroids in reducing RDS in preterm human infants had been completed (28). Since the 1970s, multiple clinical trials have demonstrated the effectiveness of antenatal glucocorticoid treatment of women in preterm labor in reducing the incidence and severity of RDS (29). Although significant concern has been raised regarding the association of postnatal steroid treatment of preterm infants with poorer neurodevelopmental outcomes, there has been no consistent evidence that administration of antenatal corticosteroids results in neurodevelopmental delay (30,31).

The identification of genetic mutations that result in lethal respiratory failure in newborn infants has led to the discovery of genetic polymorphisms associated with an increased risk of respiratory distress in the premature newborn (32). Polymorphisms associated with an increased risk of RDS in preterm infants have been identified in the surfactant protein-A, surfactant protein-B, surfactant protein-C, and the ATP-binding cassette transporter A3 (ABCA3) genes (33–35). Additionally, polymorphisms associated with preterm RDS have also been identified in genes not directly related to surfactant synthesis and secretion including mannose-binding lectin, interleukin-10, and the G protein-coupled receptor for asthma susceptibility (36–38). Elucidating the interactions between and among genetic variants, environment, and developmental factors may lead to novel management strategies in preterm infants with RDS.

LATE PRETERM NEONATES

Terminology and Epidemiology

An expert panel convened by the National Institute of Child Health and Human Development in July, 2005, recommended that infants born between 34 0/7 weeks (day 239) and 36 6/7 weeks (day 259) of gestation be referred to as late preterm (39,40). Late preterm infants account for 360,000 of more than 4 million births in the United States (40). Davidoff and Dias et al. found that two-thirds of the last decade's increase in the rate of all preterm births was associated with an increase in the rate of late preterm births. Also noteworthy was that 74.1% of all singleton preterm births in 2002 occurred at 34, 35, and 36 weeks of gestation (41). Late preterm births also accounted for 61% of preterm multiple births (41). Since late preterm infants constitute such a large proportion of preterm infants,

Table 1 Neonatal Infections by Timing of Onset

Onset	Transmission	Risk Factors	Predominant Organisms
Early Birth to 2–7 days	Vertical	Maternal colonization/infection Prolonged premature rupture Prematurity	Group B <i>Streptococcus</i> <i>Escherichia coli</i>
Late >2–7 days to 1 month	Horizontal Vertical less common	Invasive hardware/procedures (vascular catheters, endotracheal tubes, surgery) Environmental contact Prematurity	Coagulase-negative staphylococci <i>Staphylococcus aureus</i> <i>Escherichia coli</i> <i>Pseudomonas species</i> <i>Candida</i>

even a modest increase in their birth rate can have a significant impact on infant outcomes and health-care costs. Maternal and fetal indications commonly associated with late preterm delivery include pre-eclampsia, multiple gestation, and abnormal presentations (42). A portion of late preterm delivery may be preventable, especially those births that result from “maternal preference” (43,44).

Morbidity

Although historically called “near term,” multiple morbidities associated with delivery between 34 and 37 weeks of gestation including respiratory distress, temperature instability, hypoglycemia, hyperbilirubinemia, apnea, seizures, and feeding problems, as well as higher rates of rehospitalization suggest that infants at these gestational ages are not prepared for successful fetal–neonatal transition (39,45). For example, temperature instability, hypoglycemia, and jaundice were observed more frequently in late preterm infants (10%, 15.6%, and 54.5%, respectively) than term babies (0%, 5.3%, and 37.9%, respectively) (45). Similarly, poor feeding was observed more frequently in late preterm than term infants (77.8% vs. 45.3%). Apnea and bradycardia are seen in late preterm infants (45) with prevalence rates as high as 10% (46). Late preterm infants are more likely to be evaluated with a complete blood count and blood culture and treated with antibiotics for 48 hours or 7 days compared with term babies (45) due to the difficulty of excluding sepsis as an underlying cause for multiple transitional symptoms including respiratory distress, hypothermia, and poor feeding. Delay in discharge among late preterm infants is more common as a result of these problems, with poor feeding as the most common reason for the delay (45). Respiratory complications are also prevalent among late preterm infants. The most common respiratory diagnoses among late preterm infants who require assisted ventilation include RDS, MAS, and pneumonia/sepsis (20). When compared with infants born at 37 to 42 weeks of gestation, the frequency of RDS is greater in late preterm infants (62% vs. 43%), while the frequency of MAS is less (1.3% vs. 9.7%) (20). Earlier studies also demonstrate increased need for mechanical ventilation as gestational age decreases among late preterm infants (1). Need for extracorporeal membrane oxygenator (ECMO) therapy for respiratory failure among late preterm infants has also been increasing (47). Among 15,590 infants in the Extracorporeal Life Support Organization National Registry treated with ECMO between 1989 and 2006, 2258 (14.5%) were late preterm infants (47).

Death is more common in late preterm infants than term infants: risk of early neonatal death (birth to 28 days of age) is

5.2-fold greater, late neonatal death (28 days to 1 year of life) is 2.9-fold greater, and total infant mortality (all deaths from birth to 1 year of age) is 2.5-fold greater (39,48). Risk for increased morbidity also persists as evidenced by increased emergency department visits and rehospitalizations (49–51). Studies by Kinney et al. suggest that although the brain is more mature in late preterm than very preterm infants, it is still immature and can be disrupted or damaged by late preterm delivery (52). Substantial brain growth occurs between 34 and 41 weeks of gestation in utero: brain size increases by 33% in the final 6 to 8 weeks of gestation accompanied by a fivefold increase in brain volume. Late preterm infants can also develop periventricular leukomalacia, a white matter injury marker for subsequent cerebral palsy. The exact prevalence of brain pathology is unknown as systematic brain imaging is not currently recommended at this gestational age (52). Longer term follow-up studies suggest that late preterm infants are at increased risk for lower reading and math scores from kindergarten through elementary school and for participation in special educational programs (53).

Conclusion

Late preterm infants are at significantly greater risk for short-term and long-term morbidity and mortality than was previously recognized.

NEONATAL BACTERIAL SEPSIS

Despite improvements in perinatal and newborn care, sepsis continues to be a leading cause of neonatal mortality, ranked sixth among causes of neonatal deaths in the United States (54). Neonatal sepsis refers to systemic infections that occur in infants <1 month of age. While infection with bacterial, viral, or fungal organisms may present identically in the newborn infant, this section will focus on bacterial infections. Among developed countries, the reported incidence of systemic bacterial infection ranges from 1 to 8 per 1000 live births (55,56), with increasing incidence as birth weight decreases (55,57). Neonatal sepsis is typically classified by timing of onset: early-onset sepsis (EOS) occurs from birth to a week of life, and late-onset sepsis (LOS) after the first week through the first month. The two categories differ not only by age of onset, but also by mode of transmission, risk factors, and causative organism (Table 1). For EOS, despite recent advances in preventing perinatal transmission with selective intrapartum chemoprophylaxis (see Chapter 74), group B *Streptococcus* (GBS) continues to be the most common causative organism. As the incidence of GBS has decreased,

the contribution from *Escherichia coli*, particularly among the very low-birth weight population (VLBW, <1500 g), has increased. These two organisms account for 60% to 70% of all EOS (55,58,59). Other less common pathogens include *Enterococcus* species, *Streptococcus viridans*, *Staphylococcus aureus*, a variety of gram-negative bacilli, and *Listeria monocytogenes*. For EOS in VLBW infants, the profile of organisms has recently changed. Gram-negative organisms are now the predominant causative organisms with ampicillin-resistant *E. coli* accounting for approximately 40% of cases (60,61). Gram-positive organisms including GBS and coagulase-negative staphylococcus (CONS), account for another 45% of EOS cases among VLBW infants.

In LOS, gram-positive organisms predominate in all weight and gestational-age categories. For infants discharged from the hospital, the incidence of LOS caused by GBS has remained unchanged despite the use of intrapartum prophylaxis (62). In addition, LOS also occurs commonly in infants who require prolonged hospitalization in the neonatal intensive care unit (NICU). Gram-positive bacteria are the primary causative organisms with CONS accounting for approximately 40% of cases (55,60). Other organisms include *S. aureus* with increasing frequency of methicillin resistance (MRSA), *E. coli*, and other gram negatives.

The clinical presentation of sepsis in the newborn is distinct from older children and adults. Signs and symptoms may often be subtle, nonspecific, and similar to a variety of neonatal illnesses. Common manifestations include temperature instability, tachypnea, lethargy, apnea, poor feeding, and abdominal distention (63,64). Temperature instability is more commonly manifested as hypothermia, although temperatures above 37.8°C can be significant in a newborn infant when not associated with iatrogenic causes. The overlap of symptoms with respiratory, gastrointestinal, central nervous system, and metabolic disorders means that septicemia should be part of the differential diagnosis for infants with any of these findings.

The definitive diagnosis of sepsis is made by isolation of microorganisms from blood. Diagnosis by blood culture, however, is limited by test sensitivity, blood volume drawn, and can be contaminated by skin flora that may also be pathogenic in this population (65,66). As a result, diagnosis and treatment are often based on a combination of clinical symptomatology and other diagnostic markers. Evaluating the white blood cell count and peripheral differential is an important first step in assessment but has variable sensitivity and poor specificity (67). Additional hematologic parameters include the absolute neutrophil count and ratio of immature to total cells within the neutrophil series (I:T ratio) (67). Evaluation of biochemical markers associated with the host inflammatory response, such as C-reactive protein (CRP) (67,68), may also be used. CRP requires 8 to 10 hours for synthesis making it much more sensitive in the later phase of infection. Serial CRPs (two levels obtained 24 hours apart, 8–48 hours after presentation) have a reported sensitivity of 80% to 90% and negative predictive value of 99% (69). The low sensitivity of CRP early in sepsis progression makes withholding initiation of antibiotics based on a low, early CRP value inadvisable, but serial CRPs may be useful in determining the duration of antibiotic course.

Approximately one-fourth to one-third of infants with sepsis also has meningitis (70). Among symptomatic infants,

consideration of performance of lumbar puncture for examination and culture of cerebrospinal fluid is important as meningitis (pleocytosis, increased protein, hypoglycorrhachia, and positive culture) will determine duration and type of antibiotic treatment. Because viral and bacterial infections may present similarly, testing for viruses, particularly herpes simplex virus, in blood and spinal fluid should also be considered (see Chapter 74). Beyond the first few days of life, evaluation and culture of urine by catheterization or suprapubic bladder aspiration are also indicated to identify potential urinary tract foci of infection. Additional testing should be based on clinical findings and may include radiologic evaluation of the chest and abdomen.

Rapidity of progression of sepsis in the newborn infant requires prompt initiation of antibiotics once cultures have been obtained. The choice of empiric antibiotic therapy should be based on the timing and setting of infection (EOS vs. LOS, community vs. NICU) as well as the profile of microorganisms and their susceptibility patterns among specific populations. For EOS, a combination of ampicillin and gentamicin is frequently used. If meningitis is suspected, consideration should be given to addition of cefotaxime for its improved cerebrospinal fluid penetration. For LOS, therapy should be tailored to the individual patient, her/his risk factors, and past microbial flora. The frequencies of CONS, MRSA, and gram-negative organisms have resulted in the common use of vancomycin and an aminoglycoside. A worsening clinical course should result in consideration of broadening of coverage to include *Pseudomonas* species, drug-resistant gram negatives, and common fungi (e.g., *Candida*). Isolated bacteremia without meningitis or other focus is treated with 7 to 10 days of antibiotics. Treatment is otherwise largely supportive, with close monitoring and intervention for respiratory failure, hypotension, and central nervous system disturbances. Given the compromised immune response of the newborn infant, several immunologic therapies have also been investigated (71–73) of which only intravenous immune globulin has demonstrated a statistically significant reduction in mortality in cases of subsequently proven infection (71).

NEWBORN SCREENING FOR METABOLIC DISORDERS

Newborn screening for metabolic disorders is the most widely performed genetic testing in the United States. Nearly all of the more than 4 million infants born each year undergo newborn metabolic screening. The specific battery of screening tests is determined by individual state statute. As of 2005, the number of different screening tests performed varied from 4 to 46 among the states (74). Funding for the screening programs and follow-up services also varies from state to state. Ninety percent of the state screening programs have a fee paid by the family or third party payer, 61% receive funds from the Maternal and Child Health Services Title V block grant, 33% rely on at least partial funding from state general revenues, and 24% receive direct Medicaid reimbursement (75). In addition to the screening programs in the United States, most developed and many developing countries have newborn screening programs (76–79).

Newborn metabolic screening was introduced in the 1960s with the development by Robert Guthrie of a bacterial assay for phenylalanine used for the diagnosis of phenylketonuria.

Table 2 ACMG Recommendations for Newborn Screening

Core panel	Secondary targets
<i>Organic acid metabolic defects</i>	
Isovaleric acidemia	Methylmalonic acidemia (Cbl C,D)
Glutaric acidemia type I	Malonic acidemia
3-Hydroxy-3-methylglutaric aciduria	Isobutyryl-CoA dehydrogenase deficiency
Multiple carboxylase deficiency	2-Methylbutyryl-CoA dehydrogenase deficiency
Methylmalonic acidemia (mutase)	2-Methyl-3-hydroxybutyric aciduria
3-Methylcrotonyl-CoA-carboxylase deficiency	3-Methylglutaconic aciduria
Methylmalonic acidemia (Cbl A, B)	
Propionic acidemia	
β -Ketothiolase deficiency	
<i>Fatty acid oxidation disorders</i>	
Medium-chain acyl-CoA dehydrogenase deficiency	Short-chain acyl-CoA dehydrogenase deficiency
Very long-chain acyl-CoA dehydrogenase deficiency	Glutaric acidemia type II
Long chain L-3-hydroxyacyl-CoA dehydrogenase deficiency	Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency
Trifunctional protein deficiency	Medium-chain ketoacyl-CoA thiolase deficiency
Carnitine uptake deficiency	Carnitine palmitoyltransferase II deficiency
	Carnitine/acylcarnitine translocase deficiency
	Carnitine palmitoyltransferase I deficiency
	Dienoyl-CoA reductase deficiency
<i>Amino acid metabolism disorders</i>	
Phenylketonuria	Benign hyperphenylalaninemia
Maple syrup disease	Tyrosinemia type II
Homocystinuria	Biopterin cofactor metabolism defects
Citrullinemia	Argininemia
Argininosuccinic acidemia	Tyrosinemia type III
Tyrosinemia type I	Biopterin cofactor regeneration defects
	Hypermethioninemia
	Citrullinemia type II
<i>Hemoglobinopathies</i>	
Sickle cell anemia (Hb SS)	Variant hemoglobinopathies
Hemoglobin S/ β -thalassemia	
Hemoglobin S/C disease	
<i>Other</i>	
Congenital hypothyroidism	Galactokinase deficiency
Biotinidase deficiency	Galactose epimerase deficiency
Congenital adrenal hyperplasia (21-hydroxylase deficiency)	
Classic galactosemia	
Hearing loss	
Cystic fibrosis	

Guthrie's other major contribution to newborn screening was a method for using a dried infant blood spot on filter paper (the eponymous "Guthrie card") that allows for easy collection and processing of a large number of samples (80). As additional assays were developed that could be performed on blood spots, the scope of newborn metabolic screening was expanded. Criteria for inclusion of a test in the screening panel include benefit of early detection due to availability of an effective treatment, availability of a test with appropriate sensitivity and specificity, and opportunity for early detection of a potentially treatable condition during the neonatal period when it might otherwise not be clinically apparent (81). Screening programs should also provide mechanisms for appropriate confirmatory testing as well as referral for counseling and management.

With the recent development of tandem mass spectroscopic (MS/MS) methods to detect metabolites on Guthrie cards, there has been a major expansion in the metabolic diseases for which screening is now available. In 2005, the American College of Medical Genetics recommended that all states begin

screening for 29 core conditions plus an additional 25 conditions (secondary targets) that can be detected by the screening methods but may not have an effective therapy or their natural history may not be well understood (82). Table 2 lists the recommended screening tests. This list includes some assays that utilize methods other than MS/MS. Although this recommendation has been controversial, it has been endorsed by the American Academy of Pediatrics (81,83,84). The American College of Obstetrics and Gynecology has also issued a supportive opinion (85). This building consensus has resulted in an increase in the number of tests included on the screening panels in most states (74). In the future, as DNA microarray technology advances and becomes less costly, newborn metabolic screening may also incorporate this technology (86).

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