Statement on the Care of the Child with Chronic Lung Disease of Infancy and Childhood

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EXECUTIVE SUMMARY

Chronic lung disease of infancy (CLDI) represents the final common pathway of a heterogeneous group of pulmonary disorders that start in the neonatal period. Often the inciting factor is bronchopulmonary dysplasia (BPD), a chronic condition that usually evolves after premature birth and respiratory distress syndrome due to surfactant deficiency. Myriad other conditions can also cause airway and parenchymal inflammation that leads to chronic airflow obstruction, increased work of breathing, and airway hyperreactivity. Usually the inciting factors are not only the underlying disorders, but also the effects of the supportive treatment, including mechanical ventilation, barotrauma, and oxygen toxicity. These aggressive interventions for serious neonatal and infant lung diseases are often responsible for much of the chronic pulmonary abnormalities that follow. There has been an evolution of the etiologies of CLDI as well; most current CLDI is seen in infants born increasingly prematurely, and represents a disorder of intrauterine inflammation and premature extrauterine lung development characterized by alveolar simplification. This is in contrast to the early descriptions of BPD, in which postnatal inflammation and fibrosis due to barotrauma and oxygen toxicity played more of a role.

These early lung disorders have far-reaching consequences that extend into childhood and beyond. In addition, they are often accompanied by precipitating and complicating conditions that are not relegated to the respiratory system; CLDI is truly a multisystem disorder. This statement reviews more recent advances in our understanding of the pathophysiology of CLDI, not only in the respiratory system but also in the multiple organ systems involved in these children. The current approaches to diagnostic evaluation of CLDI and its complications are reviewed, and specific interventions based on understanding pathophysiologic mechanisms are discussed. Throughout, an interdisciplinary approach to the care of these children is emphasized. Finally, future directions for clinical research leading to better understanding and more effective prevention and treatment of CLDI are suggested.

I. INTRODUCTION, DEFINITIONS, AND EPIDEMIOLOGY

A. Introduction

Chronic lung disease of infancy (CLDI) is a heterogeneous group of respiratory diseases of infancy that usually evolves from an acute respiratory disorder experienced by a newborn infant. CLDI most commonly occurs in infants with birth weights less than 1,500 g, and especially in those with birth weights less than 1,000 g and who are treated for respiratory distress syndrome (RDS). However, any disorder that produces an acute lung injury and/or requires treatment with positive-pressure mechanical ventilation and high concentrations of inspired oxygen during the initial weeks of life predisposes the infant to the development of CLDI. Therefore, in addition to RDS, conditions that have resulted in CLDI include pneumonia/sepsis, meconium aspiration pneumonia, pul-

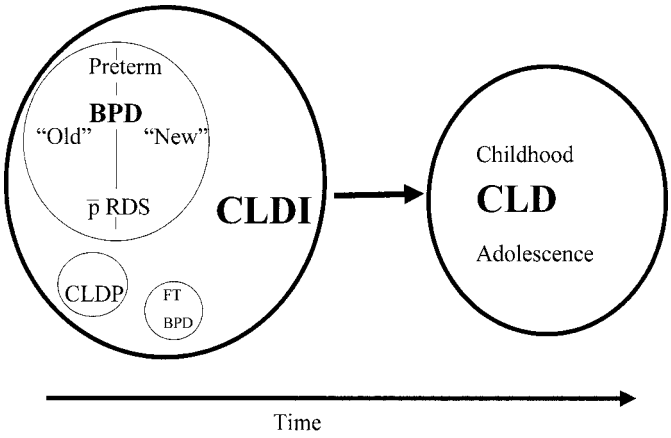

Figure 1. Proposed nosology of chronic lung disease of infancy. The term bronchopulmonary dysplasia (BPD) best describes chronic lung disease subsequent to oxygen and/or ventilator therapy for respiratory distress syndrome (RDS) in preterm newborns. Some full-term newborns can have BPD subsequent to mechanical ventilation for other neonatal respiratory conditions. Chronic lung disease of prematurity (CLDP) is sometimes used interchangeably with BPD, but this term is best reserved for other chronic lung diseases of the preterm infant that can arise after an initial period without an oxygen or ventilatory requirement. All these disorders are types of chronic lung disease of infancy (CLDI), which can evolve after infancy into CLD of childhood and adolescence. FT = full-term; p̄RDS = post–respiratory distress syndrome of prematurity.

monary hypoplasia, persistent pulmonary hypertension, apnea, tracheoesophageal fistula, congenital diaphragmatic hernia, congenital heart disease, and congenital neuromuscular disorders (1, 2).

The terminologies used to describe chronic lung disease arising from neonatal insults are confusing. The terms "bronchopulmonary dysplasia" (BPD) and "chronic lung disease of prematurity" (CLDP) are sometimes used interchangeably to describe chronic respiratory disease following treatment for RDS in preterm infants. A National Institutes of Health (NIH, Bethesda, MD) workshop report suggested that the term "bronchopulmonary dysplasia" be retained in preference to "chronic lung disease," citing the lack of specificity of the latter term (3). However, the term BPD has certain histologic and pathogenetic implications associated with oxygen toxicity and/or barotrauma, which certain lung diseases of prematurity (e.g., Mikity–Wilson syndrome, or chronic pulmonary insufficiency of prematurity) do not necessarily share. Conversely, BPD can occur in infants who were born at term. Furthermore, it has been argued that BPD today (the "new" BPD) is different from the BPD described 30 years ago, as the increased survival rate among more premature infants has meant that barotrauma and oxygen toxicity are acting on increasingly immature and possibly more susceptible lungs. One proposed nosology suggests that both BPD and CLDP are forms of CLDI. When infants with CLDI grow into childhood and adolescence, it is probably more appropriate to call residual pulmonary problems simply chronic lung disease (CLD) (Figure 1). In any event, the principles of the long-term management of all these disorders are largely similar.

The purposes of this statement are to (*1*) discuss our understanding of the pathophysiology of CLDI as a rationale for treatment principles, (*2*) review the scientific basis for the care of these infants and children, and (*3*) suggest clinical research avenues that will address unresolved issues in their care.

Most of the suggestions given for diagnostic evaluation and treatment of the child with CLDI are based on review of the more recent literature and the experience of the authors. These are not clinical practice guidelines per se, which are best based on formal evaluation of large, randomized, placebo-controlled, blinded clinical trials, often including metaanalyses. Although such trials, some of which are described in this statement, are available in the neonatology literature, they deal primarily with prenatal and postnatal prevention of BPD. Unfortunately, such large clinical trials dealing with the care of established CLDI and CLD in later childhood have not been performed. Until this is the case, care for these children will have to be based on critical evaluation of the literature and experience.

B. Definitions of Bronchopulmonary Dysplasia

A working definition of BPD is necessary, because it is from BPD that the majority of cases of CLDI arise. Since BPD was first described by Northway and coworkers in 1967 (4), there has been considerable debate about the clinical and functional characteristics (and the age at which to determine these characteristics) that should be used in its definition. In 1979, Bancalari and coworkers (5) proposed three basic criteria to define BPD: (*1*) supplemental oxygen requirement at 28 days of postnatal life, (*2*) persistent abnormalities of the chest radiograph, and (*3*) tachypnea in the presence of rales or retractions. In 1989, the Maternal and Child Health Bureau (6) proposed the following diagnostic criteria for BPD: (*1*) positive-pressure ventilation during the first 2 weeks of life for a minimum of 3 days, (*2*) clinical signs of respiratory compromise persisting longer than 28 days of age, (*3*) requirement for supplemental oxygen for more than 28 days to maintain a Pa_{O_2} above 50 mm Hg, and (*4*) chest radiograph with findings characteristic of BPD.

The use of the above-defined criteria has been questioned (7–10). With advances in treatment, many infants who still require oxygen at the age of 28 days either do not require prolonged mechanical ventilation during the newborn period or do not have the characteristic radiographic changes of BPD. It has thus been suggested that simple oxygen requirement at 28 days in infants with birth weights of 1,500 g or less be used as a criterion to define BPD (7, 9).

Shennan and coworkers (8) disputed the definition of BPD based on oxygen need beyond 28 days of age. They reasoned that most BPD observed presently occurs in very low birth weight infants with gestational ages of 30 weeks or less. They thus proposed that the need for supplemental oxygen at 36 weeks postconceptional age would be a more accurate estimate of the pulmonary outcome. Other studies suggest, however, that oxygen dependence at 28 days of life remains a useful definition in predicting subsequent respiratory morbidity (11).

A National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute/Office of Rare Diseases workshop refined the definition of BPD to reflect differing criteria for infants born at gestational ages of greater or less than 32 weeks. In addition, the new definition reflects differing severities based on oxygen requirements of less than or greater than 30% $F_{I_{O_2}}$ and/or a need for positive-pressure ventilation (3).

C. Is the Prevalence of Chronic Lung Disease of Infancy Changing?

1. Incidence of BPD. It is unclear whether the prevalence of CLDI is increasing, decreasing, or staying constant. Changing epidemiology and definitions of the disorder complicate the analysis. The increased survivability of infants with the lowest birth weights, in whom the incidence of BPD is the highest (12–16), would favor an increase in the overall prevalence of CLDI (17, 18). This increased survival can be attributed to the introduction

TABLE 1. CONDITIONS UNRELATED BUT SIMILAR TO CHRONIC LUNG DISEASE OF INFANCY

Condition	Clinical Indication(s)	Evaluation
Cardiovascular abnormalities	Unusual course, poorly corrected hypoxemia, abnormal heart sounds or murmurs, edema	Echocardiogram, ECG, consultation
Cystic fibrosis	Recurrent LRI, GI disturbances, hypochloremic alkalosis, family history	Sweat chloride, genetic testing
Upper airway obstruction	Weak cry, difficulty with extubation (or reintubation)	Radiographs, visualization
Immunodeficiency	Recurrent, unusual infections	Immunologic work-up including HIV testing
Aspiration	Common in association with vocal cord dysfunction, LRIs	Barium swallow, endoscopy
Gastroesophageal reflux	Recurrent or unexplained LRI, wheezing, etc.	Barium swallow, endoscopy, pH probe, response to Rx. If patient has a tracheostomy, color food and observe secretions
Tracheomalacia	Wheezing, cyanosis with crying	Flexible bronchoscopy

Definition of abbreviations: GI = gastrointestinal; LRI = lower respiratory infection; Rx = treatment.

of the widespread use of antenatal steroids in the 1970s as well as the more recent introduction of surfactant replacement therapy, newer modes of mechanical ventilation that reduce barotrauma, better nutritional interventions, and careful monitoring of oxygen therapy. The definition of BPD used may affect the estimation of incidence. Studies using a more stringent definition of BPD (oxygen requirement at 36 weeks postconceptional age rather than at 28 days postnatal age) will suggest lower incidence rates. However, when either definition was used in a study comparing data between 1987 and 1997, the increasing percentage of survivors born at less than 32 weeks postconception in the latter period was reflected in an increased incidence of BPD in those survivors (19). A study estimated 30% of preterm infants with birth weights less than 1,000 g develop BPD (15).

2. "New" BPD versus "old" BPD. The increasing survival of very low birth weight infants may affect not only the "quantity" but also the "quality" of the subsequent lung disease. The differing pathogenesis of BPD based on postconceptional age at birth is discussed below (Section II.A.1: Lungs). Rather than a decrease in the incidence of BPD, we may be seeing a rising incidence of "new" BPD as the incidence of "old" BPD declines. It is currently unclear whether the long-term epidemiology and outcomes of children with these different forms of CLDI will differ.

D. Differential Diagnosis

There is a need to be vigilant for other conditions that are unrelated to CLDI but may mimic it to various degrees (Table 1). Usually the neonatal history will help distinguish CLDI from these conditions. However, it is important to remember that CLDI may also be complicated by these conditions, and the listed diagnostic studies are often useful in ruling out concomitant conditions.

II. PATHOPHYSIOLOGY AND PATHOGENESIS

A. Respiratory System

1. Lungs. The pathogenesis of CLDI is multifactorial. CLDI was originally ascribed to oxygen toxicity (4) and certainly prolonged exposure to high oxygen concentrations has complex biochemical, microscopic, and gross anatomic effects on lung tissues (20). The premature infant has a poorly developed antioxidant system and therefore is at risk of oxygen free radical damage (21). Free radical-mediated oxidation of proteins is demonstrated in tracheal aspirates on Days 1–6 (22) and lipid peroxidation reaches a peak on Day 5 (23). Baro- or volutrauma is also important (24), an inverse relationship being described between hypocarbia and the subsequent development of CLDI (25). Several follow-up studies have demonstrated that the most severe lung function abnormalities are found in children who required neonatal ventilation (26, 27). Pulmonary interstitial emphysema is a result of barotrauma (28) and is associated with a high incidence of CLDI (29). The immature lung is usually exposed concurrently to the dual insults of oxygen toxicity and barotrauma (30). The former, however, at least in the neonatal piglet, causes the more significant physiological, inflammatory, and histologic changes (31). All of the above-described pulmonary insults occur at a time when most preterm infants have a relative adrenocortical insufficiency, which may potentiate the inflammatory effects (32–34).

Although oxygen toxicity and barotrauma are frequently considered to be the major contributors to CLDI, other factors are also important. Many studies have demonstrated an association between patent ductus arteriosus (PDA) and CLDI, particularly in infants of extremely low birth weight (35). Infection, especially if temporally related, potentiates the effect of PDA on CLD risk (36). Late episodes of PDA in association with nosocomial infection are important in the development of CLDI in infants who initially have no or mild respiratory distress (37). Interestingly, however, neither ductal ligation nor prophylactic use of low-dose indomethacin initiated in the first 24 hours has been shown to significantly reduce the incidence of CLDI (38, 39).

The relationship between fluid balance and CLDI is controversial. A delayed diuresis has been suggested to be more common in patients with CLDI (39). In addition, infants with CLDI may receive more fluid in the first days of life (40) and it has been suggested that early sodium supplementation may impact unfavorably on CLDI because patients so treated tend to receive higher levels of parenteral fluids (41). Nevertheless, attempting to promote an early diuresis, either with diuretics (42) or albumin infusion (43), does not improve respiratory status. In addition, the data regarding fluid restriction and CLDI are conflicting (44–46), but could be interpreted as demonstrating that only fluid restriction from birth and maintained throughout the neonatal period is effective (46).

A variety of infections, including cytomegalovirus (47) and *Ureaplasma urealyticum* (48), have been associated with an increase in CLDI. A review of four cohort studies suggested the latter may be important in infants of birth weight less than 1,250 g (relative risk, 1.91; 95% confidence interval, 1.54–2.37) (49). In addition to the role of postnatal infection, antenatal chorioamnionitis may play a key role in the production of a fetal inflamma-

tory response that may lead to early pulmonary damage as a substrate for the development of CLDI (50–52). The mediators involved in this inflammatory response are discussed below.

Infants who develop CLDI can be characterized as having a respiratory deterioration following an initial response to exogenous surfactant (53). In addition, persisting abnormalities of surfactant have been described in infants who develop CLDI and in animal models of this condition. These include delayed appearance of phosphatidylglycerol (54) and deficiency of surfactant protein A (SP-A) mRNA (55). Compared with gestational age and birth weight-matched control subjects, infants who develop CLDI may be further compromised by having higher levels of SP-A–anti-SP-A antibody immune complexes (56). In addition, activated neutrophils can mediate biochemical alterations in SP-A, as well as detrimental biophysical changes (57). Infants who develop CLDI have high alveolar capillary permeability (58). Serum proteins leak into the airways and inhibit surfactant function. There is a marked rank order of proteins with regard to their potency in impairing surfactant function (59). Analysis of airway specimens has demonstrated that even at 4–7 days, infants who subsequently either die or develop CLDI have lower levels of SP-A and higher protein content than do control subjects (60). Other surfactant function inhibitors are also present in the airways; levels of glycolipids, particularly lactosylceramide and paragloboside, are increased even in the first week (61).

Regardless of the etiologic pathway, which in most infants will be multifactorial (62), there is an early inflammatory response that persists over the first weeks. This topic has been excellently reviewed by Ozdemir and coworkers (63). During the acute phase of lung injury, the insults described above initiate a host response (63). Proinflammatory cytokines (interleukin [IL]-1, IL-6, and soluble intercellular adhesion molecule) are demonstrated in lung lavage fluid as early as Day 1 and reach a peak toward the end of the second week (64, 65). During the first week IL-1β antigen concentration and IL-1 activity increase 16- and 61-fold, respectively (66). IL-β plays a central role in the inflammation, inducing release of inflammatory mediators, activating inflammatory cells and up-regulating adhesion molecules on endothelial cells (67). In addition, there are high concentrations of another macrophage-derived cytokine, tumor necrosis factor (TNF)-α (68). Both TNF-α and IL-1 induce fibroblast collagen production (69) and cause pulmonary fibrosis in animal models. TNF-α tends to rise later, the highest levels occurring from Days 14 to 28, when IL-6 activity has decreased (70).

There is also extensive release of chemokines. The α chemokine IL-8 induces neutrophil chemotaxis, particularly in combination with either leukotriene B_4 or platelet-activating factor (PAF) (71). IL-8 is increased in the bronchoalveolar lavage fluid of infants who develop CLDI (72). The β chemokine macrophage inflammatory protein-1α, which is chemotactic for monocytes/macrophages, is elevated from birth in lavage supernatants from infants who develop CLDI compared with control subjects (73).

Production of the proinflammatory cytokines TNF-α, IL-1β, and IL-8 is regulated in part by the antiinflammatory cytokine IL-10. Sequential bronchoalveolar lavage samples over the first 96 hours have demonstrated the expression of proinflammatory cytokine mRNA and/or protein to be present, but IL-10 mRNA was undetectable (74). This deficiency in the ability of lung macrophages to express antiinflammatory cytokines may predispose to chronic lung inflammation (74).

Histologic and cytologic studies of infants with CLDI have reported increased numbers of inflammatory cells known to produce lipid mediators such as PAF (75), leukotriene B_4 (76), and complement component C5-derived anaphylatoxin (76). Sulfidopeptide leukotrienes C_4, D_4, and E_4 are 10- to 20-fold higher in infants who develop CLDI compared with control subjects with RDS (77). Preliminary evidence suggests that the cysteinyl leukotrienes are also involved in the sequelae of CLDI (78). These mediators attract and activate polymorphonuclear leukocytes, and break down pulmonary vascular endothelium with subsequent leakage of proteins into small airways (76). The levels of PAF correlate with the severity of CLDI (79). PAF is one of the most potent phospholipid mediators; in nanogram quantities it causes bronchoconstriction and vascular smooth muscle constriction. As a consequence, it has been hypothesized that the elevated levels of these leukotrienes may in part mediate the pulmonary hypertension and bronchospasm seen in infants with CLDI (80).

The increase in vascular permeability also leads to movement of leukocytes, initially macrophages and then neutrophils and subsequently monocytes and lymphocytes (81), from the pulmonary vascular compartment into the interstitial and alveolar spaces (63). Direct contact between the activated cells leads to further production of proinflammatory cytokines and other mediators (63). In addition, the activated neutrophils release reactive oxygen metabolites and elastase (82), which may damage the lung. Immunohistochemical analysis has demonstrated that the inflammatory infiltration is associated with striking loss of endothelial basement membrane and interstitial sulfated glycosaminoglycans (83). Glycosaminoglycans are important in restricting albumin and ion flux, inhibiting fibrosis in fetal animals, and controlling cellular proliferation and differentiation (83). The higher levels of elastase reported in certain studies (64, 84) may be restricted to infants who had pneumonia or required prolonged hyperoxic ventilation (85), but do occur in infants who go on to develop pulmonary interstitial emphysema (86). Raised levels of collagenase and phospholipase A_2 (87) and inactivation of α_1-antiprotease by oxidative modification (88) contribute further to the unfavorable protease–antiprotease balance of infants with CLDI (78). Interestingly, in a rat model of hyperoxic lung damage, supplemental α_1-antitrypsin prevented the reduction in compliance seen in untreated control subjects (89). The inflammatory cells and elastase activity remain elevated until 5 weeks of age (64, 84, 90).

In infants not destined to develop CLDI, after the initial injury there is recovery and resolution of the inflammatory process, usually by the end of the first week (91). The infant with CLDI, however, is exposed to ongoing insults resulting in chronic inflammation with further accumulation of inflammatory cells and production of mediators (63), and may also have an inability to mount an appropriate cortisol response in a setting of ongoing lung injury at the end of the perinatal period (92). The result is lung destruction and fibrosis, the latter being a prominent feature in infants with CLDI. The fibroblast is regulated by cytokines produced by alveolar macrophages, including transforming growth factor-β and platelet-derived growth factor. TGF-β, which increases the degradation of the existing extracellular matrix, is increased in bronchoalveolar lavage fluid at 4 days of age in infants who develop CLDI (93).

It has been advanced that the pathogenesis of BPD may be heterogeneous, and that the above-described etiologic pathways may be modified according to the postconceptional age at which the infant is born (94). According to this thinking, insults that take place early in the saccular phase of airspace growth (25–40 weeks postconception) have differing consequences from those occurring in the later saccular or alveolar phase (40 weeks to 2–4 years). Classic "old" BPD, occurring in older preterm infants, is characterized by varying degrees of pulmonary fibrosis involving proximal and distal portions of the airway, necrotizing bronchiolitis, peribronchial smooth muscle hypertrophy, squamous

metaplasia, loss of ciliated epithelium and damaged ciliary apparatus, mucous gland hypertrophy with excessive mucus in the airway, vascular changes including smooth muscle hypertrophy and peripheral extension, and alveolar Type I cell injury, all contributing to atelectasis, scarring, and variation in alveolar size and shape. The alveolar destruction, reduced multiplication rate, and scarring contribute to emphysema. This form of BPD is characterized by late inflammation, more severe airway injury, and consequent heterogeneity of alveolar damage and fibrosis. There are regions of atelectasis alternating with emphysema. The alveoli served by the most damaged and obstructed airways are often the most spared, presumably having been protected from barotrauma and oxygen toxicity by the obstruction of the airways subtending them (95).

The increased survival of very preterm infants has led to the development of the "new" BPD, characterized by less severe cellular proliferation and fibrosis, but uniformly arrested alveolar development. Several lines of evidence suggest that early inflammation caused by maternal chorioamnionitis may play a key role in the development of this form of BPD. Epidemiologic studies have shown a positive association between maternal chorioamnionitis and BPD prevalence (despite a negative association with RDS) (52). Chorioamnionitis in the preterm sheep model causes decreased alveolar septation in the fetal lamb (96), an effect that can be traced to endotoxin (97). Other causes of alveolar simplification in the early saccular phase of lung development include mechanical ventilation (98), low Po_2, elevated Po_2, steroids (ante- or postnatal), cytokines, and malnutrition (99, 100).

2. Central and upper airways. Central airways include those structures amenable to study via direct visualization with a standard pediatric (3.6-mm) fiberoptic bronchoscope: these would include the airways extending from the glottis to lobar or segmental bronchi. Central airway obstruction in the infant with CLDI has been associated with cyanotic or life-threatening episodes ("BPD or CLDI spells"), chronic wheezing unresponsive to bronchodilator therapy, recurrent atelectasis or lobar emphysema, and failure to wean from mechanical ventilation or to tolerate tracheal extubation.

2.1. Glottic and subglottic damage. Endotracheal intubation has been associated with injury to supraglottic, glottic, subglottic, and tracheal tissues in newborns (101–106). Some degree of epithelial damage after endotracheal intubation is common (102, 103), ranging from focal epithelial necrosis over the arytenoid or cricoid cartilages or vocal cords, to extensive mucosal necrosis of the trachea. Early endoscopy after tracheal extubation overestimates the possibility of long-term damage. Because superficial lesions seen at the time of extubation often resolve without sequelae (105–107), the relationship between acute laryngeal or subglottic damage and development of acquired subglottic stenosis is unclear.

Acquired subglottic stenosis has been reported in 1.7 to 8% of previously intubated neonates studied retrospectively (101, 104, 108, 109), and in 9.8 to 12.8% of infants studied prospectively (107, 110). Clinical manifestations include postextubation stridor, hoarseness, apnea and bradycardia, failure to tolerate extubation, and cyanosis or pallor. Similar presentations can result from vocal cord injuries, glottic or subglottic webs or cysts, laryngomalacia, or extrathoracic tracheomalacia. Fixed lesions of the glottis or subglottis often produce biphasic stridor, whereas dynamic lesions usually cause only inspiratory stridor. Postextubation stridor is a significant marker for the presence of moderate to severe subglottic stenosis (107, 110) or laryngeal injury (105). Apnea can replace the usual sign of stridor in preterm infants, because of their easy fatigability and paradoxical response to hypoxemia (109).

Risk factors for laryngeal injury include intubation for 7 days or more, and three or more intubations (106). These same factors are also associated with acquired subglottic stenosis (107, 110). Efforts at reducing the length of tracheal intubation or avoiding intubation altogether have been associated with prevention of subglottic stenosis (111). No cases of subglottic stenosis were found among 201 premature infants when nasal continuous positive airway pressure (CPAP) was used in place of endotracheal intubation and mechanical ventilation or as an adjunct to shorten the course of endotracheal intubation (111). Although route of intubation is not itself a significant risk factor (107), numbers of reintubations were fewer when infants were intubated nasotracheally compared with orotracheal intubation (109).

Use of inappropriately large endotracheal tubes has also been shown to be an important risk factor for the development of subglottic stenosis (101, 107, 110). A tube size-to-gestational age (in weeks) ratio greater than 0.1 has been correlated with acquired airway obstruction (107, 110). In contrast, selection of appropriate-sized endotracheal tubes has been shown to decrease the incidence of subglottic stenosis as well (107, 112). With careful attention to tube size, no differences in gestational age or birth weight per se have been found between those infants who developed subglottic stenosis and those who did not (104, 107, 110).

Concomitant infection in the setting of mucosal injury has been proposed as a risk factor for subglottic stenosis (113). No data exist, however, to suggest that prophylactic or suppressive antibiotic use prevents or decreases the incidence of this complication. Preliminary data in animals suggest that use of aerosolized dexamethasone immediately after laryngeal injury may protect the airway and prevent subglottic scarring (114). How such antiinflammatory therapy might be used in infants receiving prolonged mechanical ventilation is unclear.

2.2. Tracheal stenosis, bronchial stenosis, or granuloma formation. Acquired tracheal and bronchial stenosis or granuloma formation has been reported in CLDI infants aged 3 weeks to 17 months (115–118). The incidence of this complication among all infants with CLDI is unknown, as only those with acquired lobar emphysema, persistent lobar atelectasis, or unexplained medical failure have been studied (115–122). Within such groups, however, bronchial stenosis or granuloma formation was reported in 1.2 to 36% of infants studied (115, 122).

Endoscopic findings consist of airway narrowing or occlusion by thickened respiratory mucosa or circumferential nodular or polypoid granulations in the distal trachea, often extending into main bronchi (115–117, 120). Histologically, the masses of granulation tissue are accompanied by squamous metaplasia and ulceration of the overlying epithelium, and fibrosis in the mucosa and submucosa (115, 116).

Stenosis and granulation formation may not be complications of CLDP and CLDI per se but instead may be the result of extended endotracheal intubation and vigorous suctioning techniques. Such speculation is based on the observation that lobar emphysema resolved after removal of granulation tissue (115–117, 122, 123). Similarly, because these lesions tend to occur in the distal trachea and right-sided bronchi, repeated mucosal injury from suction catheters has been implicated as the likely mechanism. Acute mucosal injury to the carina and main bronchi occurs from unrestricted or "deep" suctioning (124, 125). In one nursery, the change in suctioning techniques from deep to shallow resulted in qualitatively less severe airway damage, even though the shallow-suctioned group was younger and received a longer course of mechanical ventilation (126).

Both the design of the suction catheter and the pattern of suctioning have been related to mucosal injury (115, 125, 127, 128). The size of the catheter should be small enough so as not

to occlude the artificial airway totally, thus avoiding excessive negative pressure (usually 5–6F in newborns) (128). Catheters with multiple side holes on several planes are less likely to cause invagination of airway mucosa into the catheter than those with single side or end holes (125, 127, 128). Use of negative pressures above 50–80 cm H_2O increases the likelihood of mucosal damage and does not increase efficiency of secretion removal (129). The most important preventative measure, however, is to restrict passage of the suction catheter to the distal tip of the artificial airway, so that the airway mucosa is protected from injury (115, 125, 127, 128, 130).

2.3. Tracheobronchomalacia and acquired tracheomegaly. Central airway collapse, or tracheobronchomalacia, has been documented in patients with CLDI ranging in age from 9 weeks to 35 months (117, 118, 131–134). Tracheomalacia was found in 45% and bronchomalacia in 34% of 47 infants with CLDI undergoing flexible bronchoscopy (122). As with other central airway lesions, however, the actual incidence of this complication is not known.

Infants with abnormal central airway collapse may be asymptomatic at rest, or demonstrate homophonous wheezing, often unresponsive to bronchodilator therapy. Wheezing becomes prominent with increased expiratory effort, and cyanotic spells ("BPD spells") may result. Acquired tracheobronchomalacia is differentiated clinically from congenital tracheobronchomalacia by a history of airway intubation and mechanical ventilation. Other lesions that cause airway compression, such as vascular rings, hypertensive enlarged pulmonary arteries, and emphysematous lobes, must be ruled out.

Acquired tracheobronchomalacia in CLDI has been attributed to barotrauma, chronic or recurrent infection, and local effects of artificial airways. The immature airway is a highly compliant structure that undergoes progressive stiffening with age (135–138). In various animal models, specific tracheal compliance decreases as much as threefold between the last third of gestation and birth (135, 138). These findings parallel changes in the human neonate (136), and appear to correlate better with changes in cartilage mechanics than with passive properties of tracheal smooth muscle (139, 140). The maturational reduction of compliance results in decreased tracheal collapsibility and resistance to deformation during positive-pressure ventilation. Nevertheless, significant and sustained airway deformation can occur at pressures commonly used in supporting infants with respiratory insufficiency. Doubling of tracheal volume and significant alterations in airway mechanics were described after brief exposure of isolated tracheal segments to a CPAP of 10 cm H_2O or to a peak pressure of 25 cm H_2O (141).

The magnitude of pressure-induced deformation is directly related to the compliance of the airway and inversely related to age. It would seem that strategies aimed at limiting peak pressures or minimizing mean airway pressures, such as rapid small positive-pressure breaths, would help to prevent deformational airway changes. It should be noted, however, that similar alterations in airway mechanics occur after exposure to high-frequency jet ventilation (142). Tracheomegaly acquired after extubation has been described in very preterm neonates (birth weight less than 1,000 g) who required mechanical ventilatory support (143).

3. Cardiorespiratory control during sleep.

3.1. Respiratory and cardiac function during sleep. Several studies conducted starting in the late 1980s found that infants with CLDI experienced episodes of hypoxemia during sleep despite acceptable awake oxygen saturation (Sa_{O_2}) (144–148). Clinically unsuspected episodes of hypoxemia during sleep were documented by Garg and coworkers (145) in infants with CLDI tested at a mean postconceptional age (PCA) of 41.0 ± 0.8 weeks. Episodes of desaturation with Sa_{O_2} values of less than 90% were more common during rapid eye movement (REM) sleep than during non-REM sleep. Although abnormal pneumographic findings did not predict abnormal desaturation episodes, time spent with an Sa_{O_2} under 90% was correlated with airway resistance (145). The possibility that desaturation may be linked to impaired lung mechanics is of special importance, because hypoxic episodes in infants with CLDI may be potentiated by airway obstruction and by an inability to compensate for this abnormality (149). Furthermore, it has been suggested that a decrease in the inspired fraction of O_2 may worsen airway obstruction (150). Therefore, episodes of hypoxemia may of themselves worsen lung mechanic abnormalities in infants with CLDI. On the other hand, high levels of oxygenation have been shown to decrease airway resistance in infants with CLDI (151).

Oxygen supplementation has been shown to be beneficial in infants with CLDI. Early studies found that the pulmonary vascular bed was responsive to oxygen in these patients (152, 153). Sekar and Duke (147) reported that supplemental oxygen improved central respiratory stability in infants with CLDI, leading to decreases in central pauses and in periodic breathing episodes. Unsuspected marginal oxygenation during sleep in infants with CLDI, together with a limitation in pulmonary reserves, may divert energy away from growth. Moyer-Mileur and coworkers (154) showed that infants with CLDI with Sa_{O_2} values between 88 and 91% during sleep exhibited decreased growth. In contrast, infants with CLDI with Sa_{O_2} values greater than 92% during prolonged sleep showed better growth.

Hypoxemia during sleep can also occur in older infants and young children with a history of severe CLDI. In a study of CLDI patients aged 3 to 5 years, Loughlin and coworkers found marked, prolonged episodes of desaturation during sleep despite an awake Sa_{O_2} value greater than 93% (155). The most severe desaturation episodes occurred during REM sleep. The same finding was reported by Gaultier and coworkers, who also noted REM sleep-related increases in transcutaneous partial pressure of CO_2 and thoracoabdominal asynchrony (156).

An abnormal sleep pattern with significantly reduced REM sleep has been reported in infants with CLDI (157, 158). Harris and Sullivan (157) reported sleep fragmentation and decreased REM sleep in six infants with CLDI with baseline O_2 values greater than 90% during sleep. When supplemental oxygen was given, all six infants had an increase in sleep duration due largely to an increase in REM sleep.

The severity of abnormalities in lung mechanics correlated with the degree of thoracoabdominal asynchrony in infants with BPD as defined by Northway and coworkers (4) tested at a mean PCA of 49 ± 3.2 weeks during quiet sleep (159). Thoracoabdominal asynchrony, a well-known phenomenon during REM sleep in infants, is due to loss of rib cage stabilization as a result of inspiratory intercostal muscle inhibition (160, 161). Rome and coworkers investigated whether residual CLDI affects this phenomenon (162). Infants with CLDI studied at a mean PCA of 41 ± 4 weeks experienced more asynchronous chest wall movements than normal preterm infants during both sleep states. The relationship between thoracoabdominal asynchrony and the severity of lung mechanics abnormalities seems to override in large part the effect of sleep states on chest wall movements. In the group of infants with resolving CLDI studied by Rome and coworkers (162), asynchronous chest wall movements throughout sleep were not associated with a significant difference in oxygenation between sleep states. Asynchronous chest wall movements during non-REM and REM sleep were extensively studied in 14 young children (mean age, 32 months; range, 19–46 months) with severe CLDI (163). During non-REM sleep, thoracoabdominal asynchrony included paradoxical abdominal move-

ment during early inspiration in the majority of these patients. Expiratory muscle activity was suggested as a potential mechanism for the paradoxical abdominal movement. The severity of paradoxical abdominal movement was significantly correlated with age between 2 and 4 years of age, suggesting that the change from the circular infant-type thorax with horizontal ribs to the elliptical adult-type thorax with oblique ribs, which occurs around 2 years of age in normal children (164), may result in patterns of thoracoabdominal asynchrony similar to those observed in adults with chronic lung disease. During REM sleep, the typical pattern of thoracoabdominal asynchrony included paradoxical rib cage movement during inspiration in the study of young children with severe CLDI (163).

The influence of sleep on cardiac function in severe CLDI was assessed in five children aged 1.5 to 5 years (165). Left and right ventricular ejection fractions were determined by equilibrium radionuclide ventriculography during the different states of alertness assessed on the basis of neurophysiological criteria. During sleep, marked decreases in both left and right ventricular ejection fractions were seen in the two children with the lowest nocturnal Sa_{O_2} levels and the most prolonged paradoxical rib cage movements during inspiration. These data suggest that sleep-related hypoxemia may lead to substantial impairment in right ventricular function and to mild impairment in left ventricular function.

One study looked at heart rate variability during sleep in 10 oxygen-dependent patients with severe CLDI aged 7 to 29 months (166). The patients were studied at normal Sa_{O_2} levels (greater than 95%) and at slightly decreased Sa_{O_2} levels (90 to 94%). Abnormalities in the autonomic control of heart rate variability suggesting long-term changes in autonomic heart rate control were found. The changes were more marked at slightly decreased Sa_{O_2} levels than at normal Sa_{O_2} levels, indicating that even mild hypoxemia occurring repeatedly may adversely affect autonomic heart rate control.

3.2. Sudden infant death syndrome risk in infants with CLDI. An increased risk of mortality during the first year of life has been documented in infants with CLDI (167, 168). It has been widely cited that infants with CLDI are at high risk for sudden infant death syndrome (SIDS).

An association between CLDI and SIDS was suggested by Werthammer and coworkers in the early 1980s (169). Home pulse oximetry was unavailable and home oxygen therapy was not often used at the time. Werthammer and coworkers found that the incidence of SIDS was increased sevenfold in a group of 54 outpatients with CLDI versus a group of 65 control infants without CLDI. Infants with CLDI had Northway Stage IV radiographic changes (4). Histologic evidence of resolving CLDI was found at autopsy in all the SIDS infants with CLDI. The diagnosis of SIDS was based on the absence of any other cause of death at autopsy. This higher incidence of SIDS in infants with CLDI is at variance with a report by Sauve and Singhal (170). From 1975 through 1982, Sauve and Singhal studied the postdischarge death rate in 179 infants with CLDI and in 112 control subjects. Of the 20 deaths recorded in the study group, only 1 was ascribed to SIDS (170).

During the early 1990s, two studies on the occurrence of apparent life-threatening events (ALTEs) and/or SIDS in infants with CLDI were published (171, 172). Iles and Edmunds monitored 35 infants with chronic lung disease of prematurity defined as oxygen dependency at 28 days of postnatal age and 36 weeks of PCA. There was no control group (172). ALTEs occurred in seven cases, and one infant died unexpectedly. This infant was not receiving supplementary oxygen at the time of death; changes due to chronic lung disease were minimal and were not believed to be a significant factor in the infant's death. Gray and Rogers (171) reported follow-up data from 78 preterm infants of 26 to 33 weeks gestational age, who were discharged after being diagnosed with CLDI on the basis of the clinical criteria of Bancalari and coworkers (5). Twenty infants received home oxygen therapy. The control group comprised 78 infants matched with the study infants by birth weight categories. None of the infants died during follow-up. Seven (8.9%) of the patients versus eight (10.5%) of the control subjects experienced an ALTE. None of the infants receiving home oxygen therapy had an ALTE. These findings suggest that infants with CLDI may not be at increased risk for SIDS if they receive appropriate management including close attention to oxygenation. The treatment of CLDI has changed considerably since the early 1980s, with far greater emphasis being placed on ensuring adequate oxygenation not only at the hospital but also after discharge.

Infants with CLDI who die suddenly probably have clinically unrecognized periods of hypoxemia (145, 169, 173). Abnormal ventilatory and/or arousal responses during sleep may contribute to their death. Garg and coworkers reported abnormal responses to a hypoxic challenge in infants with CLDI with a mean PCA of 41.4 $\pm$ 1.3 weeks (174). Twelve infants with CLDI weaned from supplemental oxygen breathed a hypoxic gas mixture (inspired partial pressure of O_2 equal to 80 mm Hg) while asleep. Although 11 infants showed arousal in response to the hypoxic challenge, all the infants required vigorous stimulation and supplemental oxygen after this initial arousal response, suggesting an inability to recover from the hypoxia.

Ventilatory and arousal responses to hypoxia depend on the function of the peripheral chemoreceptors (175). These reset to a higher Po_2 level after birth (176). Hypoxia during the neonatal period has been shown to delay peripheral chemoreceptor resetting in newborn animals (177). Studies have sought to determine whether hypoxemic episodes in infants with CLDI result in altered responsiveness to chemoreceptor stimulation. Peripheral chemoreceptor function can be tested in isolation, using either the hyperoxic test (HT) (178) or the alternating breath test (ABT) (179). The hyperoxic test induces "physiologic chemodenervation" of the peripheral chemoreceptors. The decrease in minute ventilation occurring after a change in the inspired fraction of oxygen from normoxia to hyperoxia is believed to reflect an acute reduction in peripheral chemoreceptor input and, therefore, the strength of the peripheral chemoreceptor drive. The ABT delivers a rapid hypoxic stimulus to the peripheral chemoreceptors by means of breath-by-breath alternations between a low and a normal inspired O_2 fraction. Both tests are reproducible under standardized conditions (180, 181). Calder and coworkers (182) reported a reduced response to the ABT in eight infants with CLDI as compared with age-matched control infants. Katz-Salamon and coworkers designed a more extensive study involving an HT in 25 infants with CLDI and in 35 preterm infants without CLDI (183). All infants were tested during the 40th week postconceptional age. Sixty percent of the infants with CLDI lacked a hyperoxic ventilatory response. The intensity of the hyperoxic response was negatively correlated with the time spent on a ventilator and positively correlated with the time spent without supplemental oxygen. The degree of chemoreceptor activity was closely related to the severity of CLDI, with none of the infants in the most severe CLDI category (Grade III [184]) showing a ventilatory response to hyperoxia. Thus, infants with CLDI may have deficient peripheral chemoreceptor function as a result of repeated and/or prolonged hypoxemia responsible for impaired postnatal peripheral chemoreceptor resetting.

The same group investigated whether peripheral chemoreceptor responsiveness returned to normal during recovery from CLDI (185). Ten preterm infants with chronic lung disease and

absence of a response to the HT were divided into subgroups based on disease severity (184). Episodes of desaturation were recorded during sleep despite supplemental oxygen therapy. However, these episodes decreased in number with advancing age. All the infants but two, who were in the category of maximal disease severity, developed a response to the HT within the first 4 months, at a mean postnatal age of 13 weeks (range, 9–16 weeks). The two exceptions developed the response to hyperoxia at a much later postnatal age (6 and 8 months). Thus, the most severely affected infants lacked the HT response at the age of peak occurrence of SIDS. Infants with CLDI who do not have functional peripheral chemoreceptors are unable to mount a protective response against hypoxemia and may be at risk for ALTE and SIDS (186, 187).

Interestingly, whereas development of peripheral chemoreceptor sensitivity to hypoxia seems to be impaired in subjects with CLDI who have had significant repeated or prolonged hypoxemia, the converse may also be true: hyperoxia during early life may attenuate peripheral chemoreceptor function (188–190).

B. Cardiovascular System

1. Cor pulmonale. The pulmonary hypertension and resulting cor pulmonale that is present in some patients with CLDI is produced by both functional and structural changes in the lung. In addition to acute vasoconstriction caused by alveolar hypoxia, hypercarbia, or acidosis, patients with CLDI have altered pulmonary structure involving the airways and arteries. Most patients with CLDI are born prematurely with birth weight less than 1,000 g, so that altered structure occurs in an immature lung. Although studies of pulmonary structure have been limited to fatal cases (4, 24, 95, 191–201), it is reasonable to assume that similar although less severe anatomic changes occur in patients with milder forms of CLDI. Alveolar development is impaired, with a reduced number of alveoli forming with somatic growth. Because arteries accompany the airways, there is a reduced number of intraacinar arteries; this is true of both "old" and "new" BPD. The reduction in vascular number along with alveolar hypoxia contribute to structural changes in the pulmonary arteries. The arteries that are present frequently are remodeled by medial hypertrophy and abnormal extension of muscle to arteries in the periphery (those accompanying alveolar ducts and alveoli); there can also be endothelial cell injury and intimal proliferation and thickening of the adventitia that reduces the cross-sectional area of the vascular bed and increases wall stiffness. Arteries coursing through scarred regions have further reduction in external diameter. Vascular changes in more recent studies have not been as severe as reported in earlier investigations, possibly because of improved methods of mechanical ventilation (196, 199). There is structural remodeling and an attempt at normal adaptation in childhood with a trend toward decreased medial hypertrophy with age (195).

Studies of the molecular basis for the vascular changes in BPD have examined the role of vascular endothelial growth factor. These studies have suggested that lung vascular endothelial growth factor expression is decreased in BPD, and that impaired vascular endothelial growth factor signaling can contribute to the disordered vascular growth and perhaps diminished alveolarization as well (202–204).

2. Systemic hypertension. Infants with CLDI can develop systemic hypertension (195, 205–209). There is a higher incidence of this complication in patients with CLDI compared with a group of infants who had only respiratory distress syndrome (208). Between 6 weeks and 1 year of age the upper limits of normal (95th percentile) for blood pressure while awake (not crying or feeding) is 113 mm Hg, and during sleep it is 106 mm Hg (210). The blood pressure should be recorded during the inpatient and outpatient follow-up period. When systemic hypertension occurs in patients with CLDI it is usually detected in the first year of life, with a mean age of diagnosis of 4.8 months (range, 2 weeks to 15 months) (208). In one report 43% of patients developed this finding (208).

Hypotheses to explain the pathogenesis of systemic hypertension have included the potential effect of hypoxia or medications on stimulating the renin–angiotensin or adrenergic system (207, 208). There may also be altered pulmonary endothelial function as evidenced by decreased clearance or net production of norepinephrine by the lung in patients with CLDI (205). Although many of these patients had umbilical artery catheters placed in the neonatal period, the use of such monitoring is not significantly related to the occurrence of hypertension. Patients receiving steroids as part of a therapeutic program to improve pulmonary function can develop systemic hypertension (207, 211); in such a circumstance decreasing the dose, changing the route of administration (nebulized instead of oral), or discontinuation of these agents should be considered. Systemic hypertension is usually transient, lasting a mean of 3.7 months (range, 1 to 10 months) in patients not treated with antihypertensive agents (208). Approximately half the reported patients have required medical therapy, which produced normalization of the blood pressure.

3. Left ventricular hypertrophy. Patients with CLDI can develop left ventricular hypertrophy (LVH), for often unclear reasons. The incidence of this feature in this patient group is difficult to determine because LVH documented by echocardiography or autopsy is frequently undetected by electrocardiographic screening alone (167, 212). Doppler and M-mode echocardiography have shown that LV posterior wall thickness is directly correlated, and transmitted flow velocities and early diastolic/atrial contraction flow velocity are inversely correlated, with the severity of BPD (213). The contribution of LVH to the clinical course of CLDI has not been settled. If hypertrophy is severe enough, it may cause an elevation in left atrial pressure, thereby potentially contributing to pulmonary edema and the severity of CLDI (212). In one retrospective series, patients with prolonged mechanical ventilation (greater than 60 days) and late unexpected sudden death had a higher incidence of LVH than patients with a similar ventilatory course who survived (167). However, whether LVH represents an independent risk factor is unclear because these patients also had prolonged use of multiple pharmaceutical agents. The pathogenesis of LVH has been attributed to the metabolic effects of chronic hypoxemia, hypercarbia, and acidosis, which can increase cardiac output (207, 212); stimulate the renin–angiotensin system, thereby elevating afterload (95); or produce scarring of the myocardium (198). In addition, the more negative intrathoracic pressure during inspiration in these patients increases left ventricular afterload and can contribute to hypertrophy (214). Although a single identifiable cause is usually not found, patients with LVH should be screened for systemic hypertension or, with the aid of echocardiography, for left-to-right shunting via a patent ductus arteriosus or large systemic-to-pulmonary collateral vessels. Serial echocardiograms are necessary to monitor the degree of hypertrophy and the level of myocardial function.

C. Feeding, Nutrition, and Gastrointestinal System

Infants with CLDI have difficulty maintaining a rate of growth, weight gain, and development similar to that of a healthy infant of the same age. The causes of growth failure and malnutrition in affected infants include concomitant dysfunction of other organ systems (producing congestive heart failure or renal insufficiency in some infants), decreased nutrient intake (which is generally a consequence of fluid restriction, swallowing dysfunction and

fatigue during feeding, or dysphagia due to reflux esophagitis), hypoxemia, and increased requirements for energy. Infants with CLDI and tachypnea have poorer growth and increased growth hormone secretion compared with control infants and infants with CLDI and normal respiratory rates (215). In general, there is no significant impairment of nutrient absorption or digestion in these infants unless there is concomitant bowel disease or there has been bowel resection due to necrotizing enterocolitis (216).

1. Energy. An increase in oxygen consumption is present early in the illness and correlates with severity of disease. This may reflect an increased work of breathing and therefore increased energy expenditure and may lead to energy requirements greater than those of healthy age-matched infants. However, methodologic problems in investigating infants who require supplemental oxygen make the precise determination of energy expenditure in these infants uncertain at this time. Indirect calorimetry, which has been the method by which energy expenditure is measured in these infants, is inaccurate under conditions of increased $F_{I_{O_2}}$ (217). Nevertheless, investigators have demonstrated increased energy requirements in infants with CLDI and growth failure compared with similar infants who were growing well (218). The energy expended in the work of breathing only partially accounts for the observed increases in oxygen consumption in infants with CLDI and growth failure. Resting metabolic energy requirements are higher in those infants as well and also contribute to their increased energy and nutrient needs (219). Anemia of prematurity may cause increased heart rate, stroke volume, cardiac output, and shortening fraction. Although transfusion can correct these problems, it has not been shown to reduce oxygen consumption, carbon dioxide production, or energy expenditure (220). Frequent infections can increase energy needs. Medications such as caffeine, theophylline, and β agonists may also increase energy expenditure (221). The decrease in respiratory work effected by these medications may, however, balance the increase in metabolic rate.

2. Water and electrolytes. Fluid retention may significantly limit or restrict pulmonary function in infants with BPD. In the early phase of the illness, increased levels of renin, angiotensin, and aldosterone have been documented (222). In addition, humidification in the incubator, and through mechanical ventilation to greater than 80% relative humidity, reduces or eliminates the loss of water from evaporation through the respiratory tract, leading to positive free water retention. Water collecting in respiratory tubing and running down into the infant may also be a source of free water (223, 224). The water of oxidation increases with the increased substrate utilization that accompanies the increased energy requirements seen in some of these infants and also contributes to a positive free water balance (219, 225).

3. Vitamins and minerals. Specific nutrients may play a role in the protection of parenchymal tissue or in the healing of injured tissue. Vitamin A deficiency has been associated with abnormal secretions in the lung, interruption of normal water homeostasis across tracheobronchial epithelium, absence of cilia, and lack of airway distensibility. All of these changes appear to be reversible with vitamin A supplementation. Premature infants as a group have lower serum and cord blood levels of vitamin A (226, 227). Vitamin A levels also appear to decline during the first 4 months of life in infants who are not receiving vitamin A-supplemented diets. This is often the case for infants with BPD (228, 229).

Whereas early reports suggested that vitamin E supplementation may be of benefit in the treatment of BPD, a subsequent study did not confirm any specific benefit for therapeutic amounts of vitamin E (230). Finally, supplementation with inositol, a nonessential nutrient supplied at 80 mg/kg/day for 5 days, increased the survival of a group of infants with respiratory distress syndrome and lowered the subsequent incidence of BPD (231).

Infants with CLDI are at great risk for delayed skeletal mineralization and osteopenia of prematurity. Low body calcium and phosphorus stores are exacerbated by calciuretic effects of chronic diuretic therapy (232).

4. Gastroesophageal reflux. Small, fragile infants with CLDI are prone to gastroesophageal reflux, which, on occasion, may complicate enteral feeding and worsen an already compromised respiratory system by causing asymptomatic aspiration or triggering bronchospasm (118). Medications such as theophylline and, to a lesser extent, β agonists may also increase the risk (233). Whereas it is clear that uncontrolled gastroesophageal reflux can complicate the management of established CLDI, the role that gastroesophageal reflux plays in the pathogenesis of BPD lung disease is controversial.

D. Renal System

Multiple variables, including the degree of renal maturation (a function of gestational age and postnatal age), the extent of respiratory compromise, the amount and character of fluid administered, and other nonrenal obligate losses all play major roles in determining the type of changes observed in the body fluids and electrolytes.

When pulmonary insufficiency occurs, several pathophysiologic processes can indirectly or directly modify renal function (234). Direct physical factors related to the pulmonary process, such as increased thoracic pressure accompanying positive-pressure ventilation, that adversely affect cardiac output can limit the excretion of extracellular fluid and sodium. Hormonal factors appear to play a conflicting role in the regulation of salt and water balance under conditions of pulmonary insufficiency. Atrial natriuretic peptide and vasopressin are peptide hormones commonly affected by changes in lung function. Vascular resistance in the pulmonary circuit may remain elevated, resulting in a distended right atrium that, in turn, results in a chronic increase in circulating atrial natriuretic peptide levels (235, 236). Decreased glomerular filtration rate, tubular immaturity, and a generalized decrease in renal blood flow may attenuate the effects of this natriuretic peptide. Vasopressin has also been shown to be persistently elevated in infants with CLDI (237).

Drugs are capable of affecting renal salt and water handling by the premature infant. Furosemide is perhaps the best studied agent employed in the treatment of premature infants with CLDI (238–240). Furosemide clearly has been shown to increase lung compliance and decrease airway resistance in the short term, but these effects do not consistently improve oxygenation (238, 239). The repeated administration of furosemide, however, has been associated with potential side effects, including sodium, chloride, and volume depletion (241). Infants with CLDI who develop hyponatremia and hypochloremia exhibit a higher incidence of hypertension and lower growth rate including that of head circumference (208, 241).

Renal calcifications were first described in premature infants in 1982 (242). The pathogenesis of nephrocalcinosis in very low birth weight infants appears to be multifactorial. The vulnerability of extreme immaturity and the underdevelopment of renal function may be the most important variables. Hypercalciuria is common in the very low birth weight infant, yet not all develop nephrocalcinosis (242). Decreased glomerular filtration rate, low citrate excretion, and frequently an alkaline urine are in part due to the immaturity of renal function of these infants. The development of CLDI frequently requires the administration of diuretics that may cause phosphaturia and magnesium depletion, increasing calcium excretion. Even transient insults to the kid-

neys, such as hypoxia or hypotension or the use of nephrotoxic drugs, provoke tubular injury.

E. Neurologic System and Development

Children with CLDI are developmentally vulnerable. Prematurity and low birth weight predispose them to all the risks of preterm birth, including infection, poor growth, brain injury, and disorganized behavioral interactions. In addition, they are subject to developmental and behavioral effects of impaired respiratory function.

Studies on the neurodevelopmental outcome of children with CLDI are limited because CLDI rarely exists in isolation. Premature infants and children with CLDI frequently have other medical problems that impact on behavior and development, including intraventricular hemorrhage, sepsis, anemia, apnea, parenteral feeding, ophthalmologic problems, and auditory deficits. Data generated about developmental sequelae must be interpreted cautiously in that the role of each risk factor in influencing outcome may be unclear. In addition, the causes or predisposing risk factors for the prematurity may be important in the assessment of developmental outcome. Maternal age, maternal substance abuse, absence of prenatal care, pregnancy-induced hypertension, maternal infection, or other maternal medical disorders may cause prematurity and resultant CLDI. These conditions may also directly impair fetal brain growth and development during prenatal, perinatal, and postnatal development.

1. Neurodevelopmental outcome. Developmental outcome studies of children with CLDI in the first 24–30 months of life have shown that CLDI is associated with lower scores for motor and cognitive function compared with premature control children matched for gestational age (243, 244). Most of these studies used the Bayley Scales of Infant Development, which assess psychomotor development and cognitive/mental development (245). This standardized measurement reflects neurologic (especially motor) status and cognitive skills. These studies reveal that at 24 months of age, children with CLDI have a frequency of abnormal neurologic examinations that range from 0 to 38%. The prevalence of cognitive developmental problems ranges from 14 to 80% (170, 246–249). The range of deficits among the studies reflects different definitions of CLDI during the past 20 years, exclusion criteria, and rates of case dropout over time. Socioeconomic variables and different neonatal care practices also account for some of the reported differences. In outcome studies that assessed infants at 2 years of age, it appeared that neurodevelopmental outcome reflected the duration of oxygen supplementation and hence severity of pulmonary illness (8). However, studies that assess developmental outcome into the school age period show a lack of significant correlation between outcome and duration of mechanical ventilation or oxygen therapy. The primary predictor in these late outcome studies has been central nervous system injury, either intraventricular hemorrhage or infection (250).

The studies in early neurodevelopmental outcome suggest that, between 24 and 36 months of age, many children with CLDI who demonstrate abnormal motor or cognitive skills improve dramatically compared with premature control children (250). Studies have extended this observation into the school age period. An assessment of school performance and neurodevelopmental outcome among school age children with CLDI showed that outcome scores were similar to those of premature control subjects without CLDI matched for gestation and birth weight. This finding held with both the older definition of CLDI (supplemental oxygen to a postnatal age of 28 days) and the newer definition (supplemental oxygen until the equivalent of 36 weeks of gestation in preterm infants with a birth gestation of 31 weeks or less) (250–252).

TABLE 2. EIGHT-YEAR PSYCHOEDUCATIONAL OUTCOME VARIABLES, SCHOOL PERFORMANCE, AND HYPERACTIVITY FOR NONDISABLED CHILDREN WITH CHRONIC LUNG DISEASE OF INFANCY AND THEIR MATCHED PEER GROUP

Variable	BPD Group (*8 yr old; n = 36*)	Control-matched Peers* (*8 yr old; n = 36*)
IQ Score		
Full scale	101 (13)	114 (110)†
Verbal	101 (13)	111 (11)†
Performance	100 (12)	115 (10)†
Visual–motor integration	7.5 (1.9)	9.5 (2.4)†
Receptive vocabulary	97 (12)	105 (12)†
School performance‡		
Reading level	−0.8 (1.3)	+0.3 (1.1)†
Spelling level	−0.6 (0.9)	+0.0 (0.6)†
Arithmetic level	−0.7 (0.8)	−0.1 (0.6)†
Hyperactivity rating	21 (5)	13 (4)†

Definition of abbreviations: BPD = bronchopulmonary dysplasia; IQ = intelligence quotient.

Modified from Robertson and coworkers (250).

* Children matched by socioeconomic group, attendance in regular school, and with birth weight greater than 2,500 g and gestational age greater than 37 weeks.

† $p < 0.001$.

‡ School performance is expressed as grade level above (+) or below (–) grade level expected for age.

There were no significant differences in neurologic findings at 8 years of age among the children with CLDI and premature control subjects. This included assessments of cerebral palsy, visual impairment, deafness, and severe mental retardation. However, those with CLDI who required oxygen supplementation until the equivalent of 36 weeks of gestation had the highest percentage of multiple disabilities (38%). When school age children with CLDI, but without a major neurologic disability, were compared with term-matched peers on a variety of learning tests, lower scores were seen (Table 2) (250). This observation held for full-scale IQ scores; visual–motor integration; receptive vocabulary; achievement tests in reading, spelling, and arithmetic levels; and hyperactivity. Not surprisingly, premature subjects at 8 years of age, with and without CLDI, performed at lower levels on all these tests compared with full-term control children. The lower scores of children with CLDI thus appeared to be related more to prematurity than to CLDI per se (250, 253).

Measurable delays in tests for learning disabilities in the visual–motor perceptual and receptive language domains reflect lower achievement scores in school performance. Hyperactivity is often associated with the attention deficit–hyperactivity disorder. Both learning disorders and problems with attention/hyperactivity become apparent when these children are challenged to learn in regular classrooms in the first or second grade (252).

In the past decade there has been further neurodevelopmental follow-up of children with CLDI that may be more indicative of the "new" BPD. These studies raise concerns regarding both the role of BPD and its treatment with corticosteroids (254–256). While verbal and performance IQ scores do not seem to differ between children who had CLDI and preterm control subjects, children who had CLDI did have a higher prevalence of abnormal "soft" neurologic signs, including visual–spatial defects, impaired gross and fine motor coordination, and integration (243, 244, 253, 257).

2. Behavioral outcome. Behavior of infants with CLDI has been assessed infrequently. Infants with CLDI have been compared with a control group of premature infants without respira-

tory disease, using the Preterm Infant Behavior Scale at 8 weeks of age. Infants with CLDI were less socially responsive to animate and inanimate stimuli, were not as cuddly, were more easily upset with sensory stimuli, had less skill in self-quieting, were less consolable, and had higher tone and lower hand-to-mouth ability than control subjects. Infants with CLDI have been characterized as having poorer self-organization and, in general, are not as "robust" as other premature babies (251). These behavioral observations have led to individualized neurobehavioral assessments of premature infants with CLDI. Nursing interventions have been designed to encourage state regulation, preserve energy by sensitive assessment of sleep–wake patterns, planning interventions consistent with the infant's behavioral state, and organizing the physical environment in a manner that supports preservation of energy and social interaction (258).

For a number of conditions associated with prematurity, it has become increasingly apparent that socioeconomic factors play a significant role in developmental outcome studies. Since the pioneering work of Werner, Escalona, and Sameroff and coworkers (259–261), neurodevelopmental outcome studies of premature infants have supported the "double hazard" of biological and social risk. Because many preterm infants with CLDI are born into poverty, social risk factors in this group of babies are significant. A low level of maternal education, low potential income status, and unemployment are major prenatal social risk factors associated with poorer outcomes (250, 262). That these problems do not disappear when the baby leaves the neonatal intensive care unit (NICU) is apparent. In addition, referral to child protective services by a health professional after discharge from the nursery was an additional significant risk factor that influenced long-term development. Most of the referrals were a result of neglect or mild physical abuse (263).

F. Ophthalmology

There is no known direct causal link between retinopathy of prematurity (ROP) and CLDI; however, both disorders share the single most important risk factor, extreme prematurity. For both disorders, the incidence and severity of disease increase as gestation at birth decreases. In animal models, the toxicity of exogenous oxygen can cause disorders resembling CLDI and ROP (264–266). In the later management of these established diseases, maintaining good arterial oxygenation to prevent cor pulmonale in CLDI can potentially conflict with the need to carefully manage arterial oxygen levels when the retina is not fully vascularized.

Vision loss from ROP is a consequence of excessive overgrowth of new vessels in the retina and vitreous cavity of the premature infant. This neovascularization is the recovery phase following an injury to the growing vessels, much as the fibrosis seen in CLDI follows the initial pulmonary injury. In Figure 2, the proportion of retina vascularized is depicted over time in both the normal infant (upper line) and in the premature infant who is born long before the retinal vessels (that start growing at about 16 weeks of gestation) reach the edge of the retina (ora serrata).

The incomplete vessels are highly susceptible to injury, which may include prolonged (days) elevated arterial oxygen (267), as well as other severe physiologic stressors (268, 269). Once injured, there is a delay (indicated by the lack of increase in percent vascularization on the ROP line in Figure 2) before vascularization resumes. When the vessels are able to continue to grow, they do so in excess and most likely in response to large amounts of vascular growth factors produced by the avascular retina, now increasingly mature and metabolically demanding. This neovascularization is what is observed in the eye as ROP. Fortunately, the vessels in most infants' eyes are able to progress

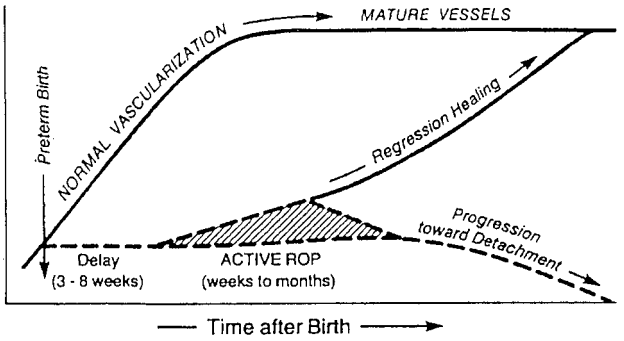

Figure 2. Diagram illustrating the progression of retinal vessels from the disk to the ora in the normal *in utero* fetus (*upper line*) and in the infant born prematurely who develops retinopathy of prematurity (ROP) (*lower line*). Normal vascularization begins at about 16 weeks and is completed around term. If initial injury to the growing vessels occurs around the time of premature birth, the rate of vascularization is slowed. The shaded area indicates the timing of active ROP, which can be observed by an ophthalmologist. Reprinted by permission from Ross Laboratories (The micropremie: the next frontier. Report of the 99th Ross Conference on Pediatric Research. Columbus, OH: Ross Laboratories; 1990. pp. 145–153).

through the neovascularization to completion. This regression is the healing phase of ROP, and can be prolonged for weeks. Animal data demonstrate that high arterial oxygen levels will slow the process of normal vascularization (266), and marginally low arterial oxygen will aggravate the amount of neovascularization following initial injury (265). (The clinical correlate of this may be the increased progression to threshold ROP in infants with established ROP treated with lower oxygen saturation targets, as discussed in Section IV.B.9: Ophthalmology.) In Figure 2, two areas are of particular interest: the time of initial injury just preceding the delay in vascularization, and the time of active ROP that includes both neovascularization and regression. These two events are separated in time. It is important to understand the differences in physiology ongoing at the two times because interventions that prevent ROP, and those that would affect the regression, are likely also to differ.

G. CLDI as a Multisystem Disease

CLDI is a multisystem disease. It is clear that there are many interactions between the pathophysiology of the various organ systems. Figure 3 summarizes the more important interactions between organ systems that have been reported in the literature and that have been outlined in this section. Figure 3 serves as a useful guide when performing an initial evaluation of the infant with CLDI.

III. EVALUATION AND DIAGNOSTIC STUDIES

A. Respiratory

1. Pulmonary. Until more recently, assessment of lung function in infants was performed only rarely. In the past 15 years, however, there have been numerous studies of developmental lung function in normal infants and comparative studies in infants with CLDI.

1.1. Lung volumes. Lung volumes in infants with CLDI and less than 6 months of age have been reported as both lower (270–272) and higher (273–275) than those of normal control infants. This discrepancy may be due to methodologic differences: studies reporting low values used helium dilution, which

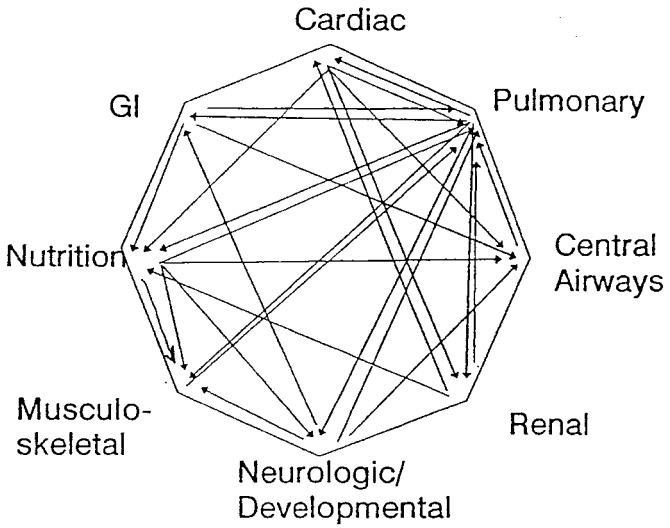

Figure 3. Interactions between organ systems in infants with CLDI. Each arrow represents an interaction that has been shown to be of significance in the pathophysiology of CLDI. For details *see* Section II (PATHOPHYSIOLOGY AND PATHOGENESIS). *Pulmonary → Cardiac*: Hypoxemia leads to pulmonary artery hypertension and possible vascular remodeling, which presents the right ventricle with an increased afterload against which to pump. Left ventricular dysfunction can also occur as a result of (*1*) decreased left ventricular filling due to rightward septal shift and (*2*) increased negative pleural pressure during inspiration due to decreased pulmonary compliance and resistance, leading to increased left ventricular transmural pressure. *Pulmonary → Renal*: ; Syndrome of inappropriate antidiuretic hormone secretion (SIADH) in infants with CLDI can reduce renal excretion of water. *Pulmonary → Neurologic*: Chronic hypoxemia can affect neurologic growth and development independent of the effects of prematurity. *Pulmonary → Musculoskeletal*: Abnormal lung mechanics can lead to diaphragmatic remodeling to more fatigue-resistant Type I fibers; respiratory muscle fatigue and chronic respiratory pump failure are seen in severe CLDI. *Pulmonary → Nutrition*: Chronic hypoxemia is one cause of failure to thrive in infants with BPD. Increased work of breathing, decreased efficiency of breathing, and chronic inflammation can all divert calories that otherwise might be used for growth. *Pulmonary → GI*: Pulmonary hyperinflation may affect diaphragmatic configuration and lower esophageal sphincter function, leading to gastroesophageal reflux. Tachypnea can lead to swallowing dysfunction. *Central airways → Pulmonary*: Excessive central airway collapsibility can lead to abnormalities in forced expiratory flow, air trapping, and hypoxemia. Abnormal lung mechanics can in turn affect airway collapsibility by increasing pleural pressure swings to which the airways are exposed. *Renal → Pulmonary*: Decreased renal excretion of water can cause increased lung water, decreased lung compliance, and increased airway resistance. *Renal → Nutrition*: Decreased renal function is associated with failure to thrive. *Renal → Cardiac*: Decreased renal excretion of water can pose an increased preload on the left ventricle. *Neurologic-developmental → musculoskeletal*: Developmental delay commonly affects muscle tone, and motor skills. *Neurologic-developmental → GI*: Swallowing dysfunction has been described in infants with CLDI, probably due to adverse oromotor stimulation combined with central nervous system dyscoordination of the swallow reflex. *Neurologic-developmental → Pulmonary*: Control of breathing may be affected in infants with CLDI, possibly because of a reset respiratory control center secondary to chronic respiratory muscle fatigue. These effects may be more marked during sleep. There may be a predisposition to SIDS. *Neurologic-developmental → Central airways*: Poor control of the upper airway and pharyngeal musculature can lead to upper airway obstruction, especially during sleep. *Musculoskeletal → Pulmonary*: Respiratory muscle weakness and fatigue can lead to chronic respiratory failure. *Nutrition → Pulmonary*: Poor nutrition as a consequence of decreased caloric intake and excessive caloric expenditure can lead to delayed lung, chest wall, and alveolar growth, delaying pulmonary healing. *Nutrition → Neurologic-developmental*: Malnutrition leads to decreased central nervous system growth and skeletal muscle weakness, which in turn adversely impacts gross motor development. *Nutrition → Musculoskeletal*: Malnutrition can cause respiratory muscle weakness and susceptibility to diaphragmatic fatigue. *GI → Pulmonary*: Aspiration due to GE reflux and/or swallowing dysfunction is a common cause for failure of the pulmonary status to improve in infants with CLDI, leading to pulmonary inflammation and bronchospasm. *GI → Central airways*: Aspiration can also lead to central airway inflammation, with subsequent homophonous wheezing, and excessive collapsibility. *Cardiac → Pulmonary*: Left ventricular dysfunction causes increases in lung water, leading to increased airway resistance and decreased lung compliance. *Cardiac → Central airways*: Left atrial enlargement can compress the left main bronchus leading to atelectasis. Airway malacia may develop in the compressed airway segment. *Cardiac → Renal*: Decreased cardiac output causes decreased effective renal blood flow, leading to renal sodium and water retention. *Cardiac → Nutrition*: Heart failure can cause failure to thrive. GE = gastroesophageal; GI = gastrointestinal.

can underestimate lung volumes in the presence of airway obstruction, whereas studies reporting increased lung volumes have used body plethysmography. One study directly comparing the two techniques in 36-week postconceptional infants showed that FRC in infants with CLDP was lower than normal when measured by nitrogen washout, but higher than in control subjects when measured by body plethysmography (276).

FRC in infants with CLDI and older than 6 months has been reported as normal (270, 277) or as increased by up to 60% (272). Longitudinal studies have demonstrated a shift from low to relatively high FRC between the ages of 1 and 3 years (278).

In summary, most studies show that lung volumes are low early in infancy and become normal or elevated later in infancy. Methodologic differences probably do not account for this change. Over time, pulmonary fibrosis may become less important relative to airway disease and, therefore, lung volumes may increase disproportionately with growth (2).

1.2. Pulmonary and respiratory system compliance. Because compliance is dependent on lung volume, the results of most studies are expressed as "specific compliance" (corrected for body weight, lung volume at FRC, or body length). Normal lung compliance is 1.2 to 2.0 ml/cm H_2O per kilogram body weight (270, 278, 279). Studies of infants with CLDI report dynamic specific compliance to be 30 to 50% of control values for infants 2 to 4 months of age (270, 272, 278, 279). Static compliance of the respiratory system in young (10 months postconceptional age) infants with CLDI, determined by the weighted spirometer technique, has been reported as 60% of control values (280). That static and dynamic compliance measurements yield similar values suggests that changes in parenchymal elastic properties alone can explain the low compliance seen in these infants, rather than altered airway properties leading to frequency dependence of compliance due to uneven parallel pathway time constants. Measurement of respiratory system compliance after the acute phase of RDS may have predictive value (281): the compliance of infants who later developed CLDI was half that of those who did not. In addition, respiratory system compliance at age 10–20 days is reduced in infants who have low maximal flows at age 2 years, and thus may be a marker of CLDI (282). As babies with CLDI grow, specific compliance improves to values of 80 to 90% of control subjects between the ages of 2 and 3 years (270, 278).

1.3. Airway function. Pulmonary resistance in infants with CLDI and less than 3 months of age, determined by the esophageal balloon technique, is more than twice that of control subjects

(270, 278, 279). Similarly, respiratory system resistance as determined by the passive occlusion technique is elevated (283). With growth, airflow resistance decreases. Gerhardt and coworkers found that mean pulmonary resistance decreased from 160 to 33 cm H_2O/L per second between the ages of 1 and 36 months (278). Size-corrected evaluation of airway function, such as specific conductance (defined as the reciprocal of resistance divided by lung volume at FRC), is more useful than resistance measurements, as it corrects for the normal decrease in resistance that occurs with growth. Specific conductance in 10-month-old infants with CLDI is about 60% predicted (277). In the study by Gerhardt and coworkers, although resistance fell dramatically in the first 3 years of life, specific conductance rose from 60% of the predicted value to only 70% predicted over the same time period (278). Similarly, size-corrected maximal flow rates at FRC in infants with CLDI are 50% of control values at a mean postnatal age of 2 months and do not increase by the age of 10 months (271). Other studies confirm that maximal flows remain persistently low through the first (284), second (282, 285), and third (286) years of life. Furthermore, those children over 2 years of age who continue to require supplemental oxygen have volume-corrected forced flow values that are less than half those of children who wean from supplemental oxygen before 2 years of age (287). The introduction of the raised volume rapid thoracic compression technique raises the possibility that airway function will be able to be monitored serially and continuously from infancy through childhood and adolescence to adulthood (288, 289).

1.4. Work of breathing. Work of breathing (WOB) is elevated in infants with CLDI. Wolfson and coworkers (290) reported that the WOB averaged 5.4 kg cm/min/kg body weight, roughly 10 times that of normal newborn infants (291). Assuming a 4% mechanical efficiency of breathing (292), this would require 5 kcal/kg body weight per day to perform. Weinstein and Oh measured oxygen uptake, and calculated that approximately an additional 10 kcal/kg per day was spent on WOB by infants with CLDI compared with control subjects (225). Thus, in an infant in whom 25 kcal/kg per day of total caloric intake is allotted for growth (293), it would appear that the WOB in an infant with CLDI may "steal" 20 to 40% of that amount. Studies that have simultaneously measured work of breathing and oxygen uptake in infants with CLDI have failed to show a relationship between these two parameters (219, 294). Thus, the increased metabolic expenditure of infants with CLDI may not be due to the elevated work of breathing alone.

1.5. Airway reactivity. Infants with CLDI have airway smooth muscle hypertrophy (295), and therefore might be expected to be more bronchodilator responsive than normal infants. Since the 1980s, 20 to 30% decreases in airway, lung, and total respiratory system resistance have been reported in response to a variety of agents, including subcutaneous terbutaline (296), nebulized metaproterenol (297), salbutamol and ipratropium bromide (283), and isoproterenol (273). These findings have been confirmed by subsequent studies (298, 299). Bronchodilator responsiveness has been demonstrated in infants with CLDI as young as 3 days of age and with gestational ages as low as 26 weeks (295, 300). Other agents have been shown to improve lung mechanics in infants with CLDI; these include theophylline (301), dexamethasone (302, 303), and intravenous, oral, and inhaled diuretics (238, 274, 279, 304, 305), although the response to inhaled diuretics has been disputed (306). There is also evidence that diuretics and bronchodilators may have a synergistic effect in improving lung mechanics (275). The effects of diuretics on airway function in CLDI may be dissociated from their diuretic effect, suggesting another mechanism of action (305).

Airway constriction due to cold air exposure has been reported in infants with CLDI (307). Hypoxic airway constriction has also been described (150, 151).

1.6. Long-term studies. Follow-up studies exist for children 6–15 years of age who had RDS and CLD as infants (262, 277, 308–328). Airway obstruction and airway hyperreactivity persist in these older children. In general, there are reductions in the average vital capacity and forced expiratory volume in 1 second compared with normal children, with an average FEV_1 about 80% of control subjects (262, 309–327). The pattern is obstructive, with a low FEV_1/VC ratio, and high ratio of residual volume to total lung capacity averaging about 130% of control subjects (262, 311–322, 324–327). There may be gradual improvement of these abnormalities over time (321). Forty to 50% of children in these studies demonstrate airway hyperreactivity to histamine, methacholine, or exercise (262, 309, 310, 321). Interestingly, infants born prematurely with and without a history of RDS, but who do not develop CLDI, also have an increased prevalence of airway hyperreactivity compared with full-term control subjects (309, 310, 328). Studies indicate that airway obstruction and airway hyperreactivity can persist into early adult life (329).

Whereas it has been proposed that the low VC and FEV_1 and the elevated RV/TLC ratio seen in children with CLD could be a consequence of premature birth itself and not of CLDI per se (312), Wheeler and coworkers (330) reported that FVC and FEV_1 were low and RV/TLC was high in children with a history of CLDI compared with premature height-matched control groups both with and without a history of hyaline membrane disease. Subsequent studies have confirmed this pattern, and it thus appears that CLDI predisposes to abnormal lung function in childhood independently from premature birth (310, 313, 314, 316, 317, 319, 320, 323, 324, 326, 329, 331).

There are few reports of lung function during exercise in children with CLD. Maximal workloads and $\dot{V}O_2$max are normal or slightly reduced (262, 311, 313, 317, 318, 324). However, limited ventilatory reserve is suggested by a low $\dot{V}E$max and a high ratio of $\dot{V}E$max to maximal voluntary ventilation (317, 324). Oxyhemoglobin desaturation during exercise has been reported (324, 327), and may be related to reduced gas transfer secondary to reduced alveolar surface area (327).

1.7. Clinical utility of pulmonary function testing. Pulmonary function testing during infancy can aid in assessing severity, response to bronchodilators and diuretics, and longitudinal improvement of lung function. Relatively few centers can perform infant pulmonary function tests, however. They require expertise in performance and familiarity with maintenance and calibration of sophisticated equipment. Short-term intrasubject variability can be high: 30% for maximal flow at functional residual capacity ($\dot{V}$maxFRC), 20–30% for pulmonary resistance measurements, and 25% for pulmonary compliance measurements (332). They require interpretation by someone familiar with not only their uses but also their limitations. Standardization of many of the techniques for assessing lung function in infants is still evolving (333–336). Finally, they usually require sedation and are expensive. Thus, although they are desirable and can add an important dimension to patient management, they will not be available at all centers.

Pulmonary function testing in older children, adolescents, and adults helps track changes in lung function with time, assess response to therapy and bronchodilators, and assess severity of pulmonary dysfunction in adulthood. Pulmonary function testing is relatively inexpensive, simple to perform, and widely available. This is especially true of simple spirometry. Spirometry should be performed in every patient with CLD who can perform the test. Studies suggest that spirometry can be reliably performed in children as young as 3 years of age (337). Pre- and postinhaled

bronchodilator administration spirometry is frequently useful, as are measurements of lung volumes and diffusion capacity.

2. Airway. Laryngeal lesions may not be clinically distinguishable from each other, and symptoms of all will be exacerbated by upper respiratory infections. Thus, any infant with a history of intubation who develops stridor should be evaluated. Direct visualization of the airways is the single best method for assessing airway problems. Flexible fiberoptic laryngoscopy permits definition of normal and abnormal laryngeal anatomy, as well as assessment of vocal cord function and dynamic events of the supraglottic airway. It can be used to approximate the degree of subglottic narrowing; the relationship between vocal cord length and the transsubglottic opening has been used to quantitate narrowing (107, 110). For detailed examination of the subglottis, however, examination under anesthesia with an operating microscope and rigid optical telescope is necessary.

Both flexible fiberoptic bronchoscopy and open tube ("rigid") bronchoscopy can be used to evaluate the trachea and other intrathoracic airways. When stenosis or granulation is suspected, rigid bronchoscopy offers the advantage of a surgical approach through the open tube. Thus, resection of tissue or balloon dilatation can be performed at the time of evaluation. In contrast, flexible bronchoscopy with conscious sedation is superior to rigid bronchoscopy under general anesthesia for the evaluation of dynamic airway events. Tracheal collapse associated with "BPD spells" can be evaluated (133), although increased expiratory effort resulting from inadequate sedation or underlying small airway disease can exaggerate airway collapse.

Radiographic techniques have also been used to diagnose central airway collapse in infants with CLDI. Sotomayor and coworkers used fluoroscopy in anteroposterior, oblique, and lateral views to document obstruction (338). Because similar radiographic findings can be induced in normal airways by creating peripheral airway obstruction (339), it is not possible to know whether these observations reflected truly collapsible central airways or secondary effects of severe small airway disease. Both diffuse and short segment airway collapse in infants with CLDI have been determined by cine-computed tomography (CT) evaluation during quiet breathing (131). Both cine-CT and high-resolution CT can be used to diagnose collapse or segmental airway narrowing, although lesions can be missed or incorrectly diagnosed by either method (340). The diagnostic accuracy of these techniques is enhanced when a combination of both is used (340).

Computer-assisted reconstruction of airway endoscopic images has enabled investigators to create three-dimensional models of airways and airway abnormalities (341). This approach, however, requires that an endoscope be passed through an airway narrowing if complete modeling is to be accomplished. When airway narrowing precludes the passage of an endoscope, radiographic imaging studies can provide information about the site and extent of the stenotic segment. The lateral neck radiograph can help to define subglottic stenosis. Tracheobronchography, using water-soluble contrast medium, has been safely used to identify the length of tracheal or bronchial stenoses while providing some information about the airways distal to the narrowed segment (342). Magnetic resonance imaging of the airway can disclose narrowing, although both fluoroscopy and CT provide more accurate information (343).

Several investigators have used tidal flow–volume loop analysis or partial expiratory flow–volume curves to detect abnormal central airway collapsibility (132, 133, 344–347). Flow limitation during tidal breathing, a reduced midexpiratory to midinspiratory tidal flow ratio, a forced-to-tidal flow at midexpiration ratio of 1 or less, and an increase in forced expiratory flow after administration of bronchoconstrictor agents all are suggestive, but not diagnostic, of central airway collapse.

3. Oxygenation during sleep and peripheral chemoreceptor function. Awake Sa_{O_2} levels do not accurately predict hypoxemia during sleep (145, 154). When assessing the need for supplemental oxygen during sleep, it is therefore best to measure Sa_{O_2} during an extended period of sleep. Short-term Sa_{O_2} measurements during sleep are not sensitive indicators of Sa_{O_2} in patients breathing room air (154). Sa_{O_2} recordings including at least 8 hours of sleep are more reliable for predicting an infant's ability to maintain a normal Sa_{O_2} value while breathing room air during sleep (154). Recording the plethysmographic waveform or the pulse amplitude modulation signals in addition to Sa_{O_2} is recommended to distinguish true drops in saturation from apparent drops due to movement artifacts or a weak pulse signal (348). As stated by the American Thoracic Society's consensus panel (349), infants with CLDI who have been taken off supplemental O_2 should be continuously monitored during sleep if they develop polycythemia, cor pulmonale, failure to thrive, or sleep pattern disruption. A full polysomnography study is indicated in infants with CLDI with symptoms suggestive of upper airway obstruction during sleep (e.g., snoring) (349).

Preventing hypoxemic episodes in infants with CLDI is probably the most effective means of preventing SIDS (145, 171). Therefore, it may be appropriate to test peripheral chemoreceptor function in infants with CLDI at discharge and when cessation of supplemental oxygen therapy during sleep is considered (178–181). Infants with CLDI with impaired peripheral chemoreceptor function should be monitored closely. Routine cardiorespiratory monitoring of infants with CLDI is not recommended, however (350).

B. Cardiologic

1. Pulmonary hypertension. The diagnosis of pulmonary hypertension in patients with CLDI requires clinical judgment and suspicion because the signs and symptoms of this complication can be masked by the respiratory disease. Palpation of a right ventricular heave or auscultation of an accentuated P_2 or murmur of tricuspid regurgitation or pulmonary regurgitation can be limited by hyperinflation and abnormal breath sounds. The detection of pulmonary hypertension can be aided by the use of noninvasive tests. Although the specificity and sensitivity of the electrocardiogram in this setting have not been established, it can be a useful method to screen for changes consistent with cor pulmonale (right axis deviation for age, right atrial enlargement, right ventricular hypertrophy). If this test is positive, serial electrocardiograms can monitor resolution of these changes, which correlate with improvement in clinical condition and degree of pulmonary hypertension (351–354). Two-dimensional and Doppler echocardiographic evaluations are useful to screen for structural congenital cardiac defects that can be overlooked in patients with respiratory disease and that can contribute to pulmonary hypertension. Patients with atrial septal defects (355, 356), patent ductus arteriosus not accompanied by a murmur (356), and hypertrophic cardiomyopathy (205) have been detected by such testing. Many infants with CLDI have had ultrasound testing in the neonatal nursery and these exams can suffice if they were thorough. Repeat studies can be considered in patients whose clinical course is atypical, including prolonged slow growth rate or extended period of oxygen dependency. The level of pulmonary artery hypertension can be assessed by the use of Doppler echocardiography if there is any degree of tricuspid regurgitation. In the absence of pulmonary stenosis, the peak velocity of flow in the regurgitant jet can be used to calculate the pressure difference between the ventricle and atrium; by then assuming a right atrial pressure of 5 mm Hg, the pulmonary systolic pressure can be determined (354, 357). In a predominantly adult study of 127 patients who underwent catheterization and echocardiography, an analyzable Doppler tracing was present in 80% of patients with elevated right ventricular pressure

(greater than 35 mm Hg) and in 57% with normal pressure. The mean difference between Doppler-estimated and catheter-measured values was 9 mm Hg (357). Serial studies are useful to assess the change in pulmonary pressure with growth or with therapy. Right-sided systolic time intervals (the ratio of right ventricular preejection period to ejection time) measured by M-mode echocardiography do not correlate with pulmonary systolic pressure or pulmonary vascular resistance (358–362). Although this interval is often prolonged in patients with pulmonary hypertension, it is also lengthened in patients with right bundle branch block or right ventricular myocardial dysfunction and is therefore not a specific indicator. Cardiac catheterization is indicated if oral, intravenous, or inhalational vasodilators other than oxygen are being tested or to screen for large systemic-to-pulmonary collateral vessels in a patient with a prolonged ventilatory course (*see* following section). However, cardiac anatomy and function as well as assessment of pulmonary pressure in ambient air and supplemental oxygen can usually be obtained noninvasively with echocardiography (354).

2. Systemic-to-pulmonary collateral vessels. Some patients with CLDI have been found by cardiac catheterization to have systemic-to-pulmonary collateral vessels arising from the internal mammary artery, subclavian artery, or descending aorta. These vessels range from small to large in diameter, are usually multiple when present, and occur in patients with normal or elevated pulmonary pressure (358, 363). Such acquired collateral vessels are known to occur in other forms of chronic pulmonary disease. Their growth may be stimulated by hypoxia, chronic inflammation with neovascularization of granulation tissue, or trauma associated with chest tube insertion (358, 363). Because the presence of a patent ductus arteriosus increases the incidence of CLDI (364–366), the presence of significant collateral vessels joining the systemic and pulmonary circulations may have a similar effect. In several patients, ligation of the collateral has improved the clinical condition, permitting weaning from mechanical ventilation (207, 363).

Patients with a prolonged ventilatory course should have a Doppler echocardiogram to assess whether there is retrograde flow of blood in the descending aorta in the absence of known runoff lesions (patent ductus arteriosus, aortic regurgitation, Blalock–Taussig shunt, aortic valve atresia) (367). Such a pattern is sensitive for collateral vessels. If there is evidence of left-to-right shunting by the Doppler study or radionuclide imaging, cardiac catheterization may be considered for precise delineation of the size and number of the collateral vessels and the degree of shunting. The contribution of these collateral vessels to the pathophysiology of CLDI has not been definitely determined. There is limited experience in closing these collateral vessels. During catheterization a large collateral vessel can be temporarily closed with a balloon-inflated catheter. If oxygenation does not deteriorate and if the vessel is judged to be contributing a volume or pressure burden to the lung, the vessel can be closed by placement of a transcatheter coil or referral for surgery can be made.

C. Nutritional

A complete nutritional history given by parents and/or caregivers is especially important. Questions should include the following: types of early and later feedings, current diet, nutritional supplements, vitamin and mineral supplements, food allergies/intolerance, appetite, chewing and swallowing problems, vomiting, diarrhea or constipation, gagging, gastroesophageal reflux, behavior related to eating, including grazing, and current and past medications. A measured 3-day diet record to assess current intake is needed with a 24-hour diet recall as a less desirable alternative. Diet analysis can be done with a computerized diet program, comparing energy, macronutrient intake, and micronutrient intake with the Recommended Dietary Allowances (368). In the acute phase, when the infant is often receiving parenteral nutrition alone, calorie needs may vary considerably and must be individualized according to weight gain. Parenteral nutrition guidelines for premature infants can be used as a reference (369, 370). In the infant with CLDI, the percentage of calories derived from carbohydrates should be ascertained to assess possible implications for CO_2 production (*see* Section IV.B.7.1: Formulas). As the infant improves clinically and begins a transition to enteral feeds, a "catch-up growth" energy equation can be used (*see* Section IV.B.7.1: Formulas).

The anthropometric measurements of length, weight, and head circumference are routinely monitored as related to gestational age-adjusted normative data. Curves exist for assessment of postnatal growth of very low birth weight children (371, 372). Although correction for preterm birth is usually made to the age of 2 or 3 years, correction for gestational age can continue to affect the growth percentiles up to age 7 years, as catch-up growth can occur to this age and beyond (373–377).

Apart from growth curves, the best ways to assess nutritional status are not known. Measures of midarm circumference, the derived midarm muscle circumference, and triceps skinfold are sometimes necessary when nutritional status is unclear (378). Standard values are available (379, 380). Assessment of wasting, stunting, and growth failure, that is, weight and height percentiles decreasing over time, is necessary. Percentage of ideal body weight based on Waterlow or similar criteria can be used for assessment (381, 382).

There are few studies on the utility of routine blood tests. Laboratory values may include albumin and prealbumin to assess energy and protein intake, reflecting that of 1 month prior and 1 week prior, respectively. Electrolytes, complete blood count with serum ferritin for iron status, alkaline phosphatase, and specific vitamin and mineral tests such as vitamin A, calcium, phosphorus, magnesium, and zinc may also be appropriate. Medications and the nutrients that may be affected should also be examined in case nutrient supplementation is required, based on current laboratory values (383).

Bone mineral content measurement by dual photon absorptiometry for diagnosis of osteopenia of prematurity, and measurement of lean body mass by total body electrical conductance and total body potassium measurements, are presently research tools only.

Few studies have accurately assessed body composition in these infants. Thus, when instruments are available to measure bone mineral density, body fat content, and lean body mass, this should be done as part of a rigorous controlled study design.

The early recognition and management of swallowing dysfunction, oral aversion, and gastroesophageal reflux is important to both feeding and growth. In infants with suspected swallowing dysfunction, video studies of the swallowing function should be performed by a radiologist and an occupational therapist who is equipped to evaluate swallowing function using different food textures. Oral aversion related to endotracheal and suctioning stimuli are common and also need to be evaluated by a feeding specialist. In symptomatic infants (and asymptomatic infants with unexplained failure to thrive) appropriate testing to rule out gastroesophageal reflux including barium swallow, gastric scintiscan, extended (24 hours) esophageal pH monitoring, and endoscopy should be performed. Evaluation for gastroesophageal reflux should also be considered in asymptomatic infants with an unexplained prolonged supplemental oxygen requirement.

D. Renal

Renal assessment is largely dependent on the child's general nutritional status, presence or absence of systemic hypertension,

and degree of diuretic usage. In general, urinalysis, electrolyte, blood urea nitrogen, creatinine, calcium, and phosphorus metabolism are monitored. When systemic hypertension is documented, an echocardiogram may be helpful to assess baseline left ventricular mass (384) and to confirm the absence of a coarctation of the aorta. Additional evaluation may include renal ultrasonography to evaluate for renal calcifications, renal radionuclide studies, intravenous pyelography, aortography, computed tomography of the kidneys or adrenal glands, or plasma and urine hormonal studies based on the clinical situation (384).

E. Neurodevelopmental

A neurodevelopmental examination by a primary care clinician should include an assessment of motor, social, language, and cognitive functions. A standard neurologic examination will detect cerebral palsy (hypertonia, hypotonia, and or weakness with increased deep tendon reflexes), strabismus, visual and hearing impairment, hemiparesis, microcephaly, and macrocephaly. A formal assessment of hearing (brainstem auditory evoked potential response) should be performed. Primary care physicians can monitor development in the office guided by standard developmental milestones, corrected for gestational age in the first 2 years. Screening tests that assess neurodevelopmental tasks (e.g., Denver II, Child Development Inventories, Ages and Stages Questionnaire), temperament (Carey Temperament Scales), and behavior (e.g., Pediatric Symptom Checklist) can be performed in primary care pediatric offices (385). Those children in whom a developmental delay is suspected should be referred for a standardized developmental assessment by a behavioral pediatrician, a clinical psychologist, or a child psychomotrist.

F. Ophthalmologic

An ophthalmologist experienced in the evaluation of ROP in premature infants should evaluate these infants according to the guidelines set forth jointly by the American Academy of Pediatrics, the American Academy of Ophthalmology, and the American Association for Pediatric Ophthalmology and Strabismus (386). The first examination should be done at the latter time period of either 31–33 weeks postmenstrual age, or 4 weeks chronological age. Subsequent examinations are based on the findings at the first screening. Infants with more than 37 weeks of gestation at birth need not be screened, nor those between 29 and 37 weeks if they had a "medically stable" course (i.e., no supplemental oxygen requirement). It is rare, however, that an infant with CLDI has been medically stable during the initial hospital weeks. A more conservative approach is to screen all infants with less than 32 weeks of gestation at birth, even if stable.

IV. TREATMENT

A. Transitioning the Child with CLDI from Hospital to Home

1. Discharge and home care planning.

1.1. Rationale and goal. Advances in perinatal care, changes in health care economics, and research suggesting a negative impact of prolonged hospitalization on development of the preterm newborn have influenced discharge practices for infants with CLDI (387). The home environment has increasingly been recognized as the optimal setting for medically stable, technology-assisted infants to receive the complex and demanding care they require (388).

Studies have documented that early discharge from the NICU with proper home follow-up is not only less costly, but also safe and beneficial for the infant and family (389–394). Rarely, the costs for infants requiring very complex care at home may exceed the costs for similar institutional services. In such cases, the other benefits of home care may still outweigh the cost differences, and this option should not be eliminated from consideration (395).

TABLE 3. AREAS OF FAMILY ASSESSMENT

Area	Description
Family structure	Single- or two-parent household
	Number and ages of siblings
	Presence of extended family
Patterns of daily living	Careers and job-related activities
	Social and recreational activities
Family dynamics	Primary caretaker
	Parents' level of involvement
	Identification of secondary care providers
	Communication patterns among family members
	Coping patterns and response to stress
Cultural beliefs and practices	Language(s) spoken
	Religious beliefs
	Child-rearing techniques
Proximity to health care services	Method of transportation
	Distance from health care providers
	Distance to closest hospital
Responsiveness to infant's needs	Performance of simple care activities
	Performance of complex care and assessments

Modified from Reference 410.

Combining the benefits of home care with optimal medical treatment and support is a challenge requiring collaboration among parents, care providers, hospitals, payers, and communities. The overriding goal of home care is the provision of comprehensive, cost-effective health care within a nurturing environment that maximizes the capabilities of the infant and family and minimizes the effects of the disabilities (396).

1.2. Assessing the potential for home discharge. Eligibility for home care should be based on a comprehensive analysis of the infant's therapeutic needs, family considerations, and available resources. Potential benefits must be carefully weighed against risks. Parents should not be pressured to accept home care if this option would be detrimental to the infant or family. The following factors should be assessed to determine appropriate candidates for home care (396).

Patient Factors. Physiologic stability and resolution of acute illnesses are imperative before discharge. Medical criteria for discharge generally include adequate weight gain and adequate fluid and caloric intake by mouth, nasogastric, or gastrostomy tube feedings. If the need for nasogastric feedings is judged as likely to be prolonged, placement of a gastrostomy tube is preferable to avoid the potential risks of repeated passing of nasogastric tubes and the possibly adverse effects of a nasogastric tube on the development of normal swallowing function. The infant must be able to maintain thermal stability in an open crib. Respiratory stability must be demonstrated by a stable requirement for supplemental oxygen to maintain appropriate saturation levels during sleep, at rest, and with activity (including feeding). Apnea must be resolved or controlled. Medication levels must be at therapeutic range and side effects documented (397). Plans should be made to explore home care as an option as soon as the infant's condition begins to stabilize.

Family Factors. Assessment of the family's potential home care capability is an ongoing process that should begin on admission. A family assessment provides information about the family constellation, functions, and roles and examines the family's specific stressors and support systems (387). Important areas of family assessment are outlined in Table 3.

While certain family characteristics are essentially static, some, such as employment schedules, can be altered. Exploring these areas will assist the family in anticipating the needs of their infant as well prepare them for potential life style changes following discharge (398).

Financial Factors. Careful assessment of the family's financial circumstances is critical. Health insurance policies vary widely in type and scope, and limits of inpatient and ambulatory benefits must be identified. Income, debts, and other financial obligations of the family must also be considered. Costs of care including equipment, supplies, nursing, physician fees, and psychosocial services require careful estimation. Hidden costs such as utilities, home renovation, and time lost from work should also be considered. The health care team must evaluate the projected cost of home-based care and the available methods of financial support. The family should be assisted with required applications for financial assistance and funding problems should be resolved before discharge. Creative financing arrangements often involve a combination of public, private, and personal financing. Because funding is a common delaying factor in the discharge process, financial planning should begin as early as possible (387, 395, 396, 399). Sources of financial aid for care of high-risk infants should be contacted and applications for assistance should be made as early as possible in the discharge process (395, 397).

Home Factors. The home environment should be assessed to determine its appropriateness and safety. The location should be considered for its proximity to medical services and emergency care. It must be accessible, with enough room for the required equipment and supplies. The electrical capability should be assessed for adequacy and potential need for a generator identified. Utilities, including heat and telephone, must be operational. The home should be equipped with smoke detectors and assessed for the presence of environmental hazards including cigarette smoke. The family should be helped to correct any deficiencies before discharge (388, 398).

Community Factors. Community resources must be available to support the family in caring for the infant at home. The health care team should assist the family to identify and access the appropriate resources. The following resources should be considered:

- *Pediatric primary care provider*: This individual should be an integral part of the discharge planning process, be knowledgeable about the home care plan, and willing to participate by providing primary care services (396).
- *Nursing services*: Many infants require in-home nursing services for 8 to 24 hours/day, depending on the severity of illness and the degree of home technology required. In addition, community health nurses are often necessary for supervision and coordination of care. The extent of pediatric experience and quality of services provided should be carefully evaluated when selecting nursing agencies.
- *Equipment vendors*: Optimally, a vendor can be identified to supply not only the oxygen but also all of the required supplies. Factors to consider in selecting vendors include extent of pediatric experience, specialized equipment for infants, 24-hour availability with reasonable response time, home visits for periodic evaluation, and equitable cost. Some insurance plans designate preferred vendors that must be utilized to ensure payment of services (400). These vendors must have pediatric equipment and expertise, for example, low-flow oxygen regulators.
- *Developmental screening and early intervention services*: Many tertiary centers offer periodic developmental screening and necessary intervention for high-risk infants. In the United States, some states also provide comprehensive services. Funding for such services may be provided through Public Law 99-457 legislation. Additional services may be solicited through local community service organizations (388, 395).
- *Educational services*: Early intervention and educational services should be provided in the least restrictive environment to promote socialization with peers and age-appropriate activities. The educational setting may require modifications to incorporate the equipment, therapeutic care, and nursing support required by the child (396, 401).
- *Respite care*: Alternatives for short-term temporary care should be identified to enable the family to meet emergency needs, obtain reprieve, or provide an alternative to institutionalization. In the United States, respite services are often provided through state departments of mental health, social services, or public health (397, 402).
- *Psychological support services*: Parents should be provided with information about support groups or individual counselors who may help them cope with the stress of caring for a medically fragile infant at home. Religious communities, clergy, other family members, or neighbors may also be able to provide social support and practical assistance as necessary (387).

1.3. The discharge process. A comprehensive, coordinated discharge process is required to facilitate transition of care from the hospital to home and arrange transfer of ongoing case management to the family and community services. This process transcends the hospital boundaries and fosters parent–professional collaboration with the interdisciplinary health care team in developing plans for care, follow-up, monitoring, and evaluation (403). Active participation by the family creates a plan that meets their individualized needs. Flexibility should be built in because the infant or family's needs or circumstances may change quickly (404).

Caregiver Training. Education for the family and other caregivers including professional and paraprofessional health care providers, and school and emergency personnel, is a critical component of the discharge process. Table 4 lists general topics for discharge teaching. The teaching plan must be individualized to meet the specific needs of the family and other care providers.

As much as possible, teaching should be done in a quiet area. Learners should be instructed in performing simple tasks before complex ones, and should have the opportunity to practice each task as often as possible. Teaching strategies should be varied and suited to the subject matter. Techniques include one-on-one teaching, printed material, audio–visual aids, demonstration, and return demonstration. The learners must demonstrate competence in all technical skills by performing the tasks. Condensing documentation of teaching onto one form expedites assessment of the teaching/learning process.

As discharge approaches, parents should assume more of the caregiving responsibilities for their infant. They should have an opportunity to assume primary responsibility for their infant's care during a 24-hour period with hospital staff nearby for support. Passes out of the unit and "field trips" out of the hospital for a few hours also help to increase parental confidence and decrease anxiety (387).

Planning and Coordination of Discharge. In addition to caregiver education, other aspects of the discharge plan require coordination. Several discharge planning meetings involving hospital care providers, the primary care physician, family and community agencies may be required to complete all aspects of the discharge plan. The following tasks should be completed before discharge:

TABLE 4. TOPICS FOR DISCHARGE TEACHING

Topic	Teaching Components
CLDI	Disease Process, Sequelae, Management
Assessment	Vital signs (temperature, pulse, respirations)
	Evaluation of color
	Breathing pattern
	Lung auscultation
	Fluid balance, skin turgor
	Neurologic status
	Changes in appetite, behavior
	Use of cardiorespiratory monitor (if needed)
Well-child care	Bathing, diapering, skin care
	Immunizations
	Development and stimulation
	Car, home safety
Nutrition	Feeding schedule, importance of weight gain
	Formula preparation
	Methods of feeding
	Techniques to maximize oral feeding
	Nasogastric/gastrostomy tube feedings
	Use of enteral feeding pumps
	Antireflux measures
Medications	Name, purpose
	Dosage, route, frequency
	Method of administration
	Side effects
	Omitting or repeating a dose
	Storage, safety
	Indications for PRN medications
Oxygen	Purpose, flow rate
	Method of administration
	Reading the flow meter
	Maintenance and cleaning of equipment
	Weaning procedure
	Oximetry technique and interpretation
	Safety considerations
Pulmonary treatments	Purpose, frequency of treatments
	Methods to clear secretions, bulb syringe, suction
	Nebulizer technique
	Chest physical therapy
Infection control	Minimize exposure, day care issues
	Handwashing technique
	Care providers to receive influenza vaccine
Tracheostomy care (Refs. 502, 567, 568)	Suctioning technique
	Humidification
	Changing the tracheostomy tube
	Skin care
	Techniques to facilitate speech
	Care, cleaning of the tracheostomy tube
	Safety considerations, emergency management
Mechanical ventilation (Refs. 516, 569–572)	Principles of operation
	Settings
	Operation, maintenance, cleaning of equipment
	Troubleshooting equipment
	Schedule for ventilation, weaning
	Response to alarms
	Safety considerations, emergency management
Emergency management	When and who to call for symptoms
	Procedure for emergency assistance
	CPR technique
	Telephone numbers posted near phone
Anticipatory guidance	Emotional and social needs of family
	Sibling rivalry
	Rehospitalization
	Alternatives to home care
Travel	Transport bag with emergency supplies
	Portable suction machine
	Air travel with oxygen (Ref. 573)

Definition of abbreviations: CLDI = chronic lung disease of infancy; CPR = cardiopulmonary resuscitation; PRN = *pro re nata* (take as needed).

From Baker and coworkers (387), Colangelo and coworkers (397), and McCarthy (399).

- Organization of the infant's daily schedule for convenience
- Completion of all teaching with documentation of caregiver response
- Completion of all necessary referrals to community agencies and follow-up services
- Securing of necessary equipment and supplies
- Coordination of timing of postdischarge visits to specialists and primary care provider
- Verification that medications are available at the local pharmacy
- Notification of rescue squad and utilities of high-priority household
- Development and compilation of written discharge instructions and materials for the family
- Completion of a comprehensive discharge summary

A written care plan and supplemental materials regarding key aspects of the infant's care should be provided to the family to help organize the care at home. The family should be advised to post emergency numbers with their own address, phone number, and cross streets near their telephone. Telephone numbers of the pediatrician, equipment company, specialists, and nursing agencies should also be readily available. A comprehensive discharge summary including pertinent history, hospital course and recent laboratory results, growth parameters, and immunizations should be provided to the family, primary care provider, and involved agencies. The family should also be provided with a copy of the most recent chest radiograph (388).

Evaluation and Follow-up. Evaluation is a crucial component of the discharge planning process. Frequent telephone contact after discharge can determine whether the family has been able to adapt to the new routine, if equipment vendors and nursing agencies have provided the referred services, if the family has kept follow-up appointments, and if the family has questions about the infant's care. Telephone contact or home visits can be utilized to reinforce teaching, provide emotional support, direct the family to appropriate resources, and assist them to make necessary adjustments to the home care regimen. Communication with community care providers and agencies should solicit their feedback about the effectiveness of the discharge process. Any rehospitalizations should be analyzed for problems related to teaching or with the discharge plan (387, 388).

2. Family impact. Home care generally creates a mix of positive and negative emotions for the parents. The unity of the family unit is reestablished with the infant's discharge. Time-consuming hospital visitations are eliminated and parents have an opportunity to watch their infant develop and thrive in the home environment. Siblings can participate in social and caregiving activities with the infant. Parents gain a sense of accomplishment in their caregiving activities. They come to realize that they can best respond to their infant's needs, and begin to feel more in control of their situation (398).

Potential negative effects have been well documented, including caregiver fatigue, social isolation, marital conflict, anxiety regarding potential problems, sibling difficulties, and financial demands (394, 398, 405). Stress may result from issues of privacy, confidentiality, and conflict with professional care providers in the home (406). Studies have suggested that home care for medically fragile children carries a high emotional cost for parents unless adequate social and financial support is provided (394, 407).

Anticipatory guidance should be provided about the potential impact of home care on family dynamics, activities, and schedules, including work-related activities. Through discussions of these issues, families can identify possible approaches before discharge and appropriate community resources can be accessed.

Open lines of communication between both parents and the professional care providers are essential to clarify roles and expectations and facilitate successful adaptation. Peer support through participation in a parent group or network is helpful for many parents. Continued psychosocial assessment is required throughout the duration of home care as the condition of the infant and family dynamics change.

3. Case management. Case management services are being used increasingly as a means to ensure comprehensive, family-centered, community-based programming for medically fragile children and their families. The primary goal is to ensure continuity for the child and family across hospital, home, educational, therapeutic, and other settings. Case management should ensure that the health needs of the child are met and that financial issues, psychosocial concerns, and educational needs of the child and family are addressed. Case management is most effective if a single individual is designated to manage the coordinated care over time (408).

Key elements of the case manager role include the following: (*1*) assessment of the needs of the child and family for resources and support, (*2*) accessing and development of necessary resources, (*3*) coordination of services, (*4*) monitoring and evaluation of service provision and cost, and (*5*) family advocacy. Clinical expertise, community awareness, expert communication, and problem-solving skills are required in the case manager role (408, 409). Case management should promote the family's role as primary decision maker. Families may choose to be involved to varying degrees in case management activities. Many parents take on increasing responsibility for care coordination over time, and they should be encouraged and supported in this role (404, 409, 410).

3.1. Medical case management. Comprehensive case management should not be confused with medical case management, which is essential for the safe management of medically fragile infants at home. Medical case management requires a designated coordinator of the health care team who is knowledgeable and available to make timely evaluations and decisions about changes in the patient's medical status. Medical case management includes the following: (*1*) monitoring and revision of the medical care plan, (*2*) revision and certification of the continued need for medical equipment, (*3*) reassessment of the required levels of care and frequency of medical tests, (*4*) adjustment of ventilatory support, drug therapy, nutrition, and other care, (*5*) referral for specialized services and medical consultation, and (*6*) decisions regarding hospital readmission (404).

4. Alternatives to home care. Alternatives to home care may require consideration based on a through evaluation of the needs and wishes of the family and the expected course of the illness. Examples of alternative settings include rehabilitation centers, chronic care facilities, specialized foster care, and hospice programs. These alternative settings should be considered if the assessment areas in Table 3 reveal any factors prohibitive to the child's care in their current home environment, or if the family is unable to demonstrate adequate competency in the areas of learning outlined in Table 4. Furthermore, as the level of intensity of home care increases, some families may not be able to cope with the burdens imposed. While most families are able to accommodate certain levels of home technology such as nebulizers, supplemental oxygen, and pulse oximeters, home mechanical ventilation can impose another level of commitment. As home medical care becomes more complex, additional psychosocial stressors (two working parents, additional siblings, etc.) take on added significance, and should be accounted for when deciding whether the child is best placed at home or in an alternative setting. These settings should be carefully chosen with consideration given to whether the goals are subacute, rehabilitative, or chronic care.

B. Specific Interventions

1. Bronchodilators. Bronchodilators have become part of the standard therapeutic regimen for infants with moderate to severe CLDI because improvements in pulmonary function have been demonstrated after treatment with bronchodilators belonging to methylxanthine, β-sympathomimetic, and anticholinergic families.

Several groups have demonstrated that β agonists can cause short-term improvements in lung function (283, 297, 411) and blood gases (412) in ventilator-dependent infants with early CLDI. Aerosolized β sympathomimetics, including isoproterenol, terbutaline, albuterol, and salbutamol, appear to improve pulmonary function by reducing bronchospasm; improvements in pulmonary function measurements have included increased dynamic compliance, increased specific airway conductance, increased forced vital capacity, and decreased airway resistance (273, 283, 296, 298, 411). Theophylline has been shown to relieve bronchospasm and therefore decrease airway resistance and increase compliance (275, 301). Caffeine, another methylxanthine, has also been shown to improve pulmonary function in infants with CLDI (413), and is commonly used in the NICU for the treatment of apnea of prematurity. In addition, the methylxanthines can improve diaphragmatic contractility (414). Orally administered theophylline and caffeine can have significant side effects (tachycardia, gastroesophageal reflux, altered sleep and behavior patterns), and thus, in general, the use of inhaled bronchodilators is preferred, especially after NICU discharge, once the risk of apnea of prematurity is past. If methylxanthines are used, strict attention should be paid to dose, and serum levels should be monitored (5–15 mg/L for theophylline, 5–20 mg/L for caffeine), as the therapeutic window can be quite narrow for these agents. Anticholinergic agents (e.g., atropine, ipratroprium) can affect bronchodilation in this population (283, 298, 415), with synergism noted between ipratropium bromide and salbutamol (416). Bronchodilator responsiveness, however, is not universal and in one study no relationship was noted between a positive response to a β agonist and either postnatal age or postconceptional age (417). Drug dose is one possible explanation for the apparent treatment failure seen in certain infants; whereas 200 μg of salbutamol given via a metered dose inhaler (MDI) and spacer improved compliance and resistance in all patients in one study, a universal effect was not seen if a lower dose of 100 μg was used (418). Many studies have examined only the acute effect on lung function of a single dose of bronchodilator. Repeated doses of salbutamol given to ventilator-dependent infants from as early as the first week have also been associated with improvements in static compliance; the effect was independent of postnatal age (411). Nevertheless, trials to date have not demonstrated that in ventilated infants regular bronchodilator therapy improves long-term outcome (419). Until such evidence is available, a reasonable course of action might be to restrict such therapy to symptomatic patients, for example, those with obvious bronchospasm that is interfering with effective ventilation, displaying such symptoms of increased work of breathing as prolonged expiratory phase or use of accessory muscles of respiration. Although β-agonist drugs have been reported to increase mucociliary clearance, there are no studies demonstrating this effect in infants with CLDI.

In non–ventilator-dependent patients (300) and in infants seen at follow-up (273, 298, 420), bronchodilators can result in acute improvements in lung function: a reduction in airway resistance and an increase in specific conductance, but not changes in thoracic gas volume or dynamic compliance (273).

No synergic effect on airway resistance or maximal expiratory flow at functional residual capacity, however, has been noted between inhaled metaproterenol and atropine (298). In prematurely born infants, with or without CLDI, the acute effect of nebulized bronchodilator therapy at follow-up is variable. Although there may be an influence of postnatal age (421), more consistent relationships with a response to therapy are positive symptom status and lung function abnormalities (420, 422, 423). In symptomatic, prematurely born young children regular terbutaline (424) or ipratropium bromide (425) via an MDI and spacer improves lung function and reduces the occurrence of symptoms at follow-up.

When using bronchodilators in infants with CLDI, the method of administration is an important consideration. Although intravenous salbutamol causes rapid improvements in lung function, this is associated with tachycardia (426). In both ventilated and nonventilated infants (427), there is a low deposition of bronchodilator drug regardless of whether this is given via a nebulizer or MDI and spacer. In addition, the deposition is variable and favors central lung regions (427). Delivery from an MDI has several advantages over nebulization; it takes a shorter time, does not require adjustment of the ventilator flow, or cause cooling of gases (427). In addition, in symptomatic premature infants studied at follow-up, although via both delivery techniques similar levels of bronchodilation were achieved after 15 minutes, delivery by an MDI and spacer avoided the paradoxical deterioration in airway resistance seen 5 minutes after nebulization (428). The paradoxical response is not consistently seen and, as the infants likely to be so affected are not predictable (429), use of an MDI and spacer may be preferable. Whether inhaled drugs are given by MDI and spacer or nebulizer, a face mask helps ensure optimal drug delivery.

Because the response to bronchodilators in infants with CLDI is variable, infant lung function testing may be a useful way to identify bronchodilator-responsive infants likely to benefit from chronic bronchodilator treatment (417, 430).

2. Antiinflammatory drugs. Corticosteroids given postnatally, specifically dexamethasone, facilitate weaning from mechanical ventilation and extubation in most infants with BPD and have become the most common pharmacologic agents used to treat infants with evolving BPD and established CLDI. Although initial studies enrolled infants with BPD defined by oxygen dependence at 28 days of age and an abnormal chest radiograph, more recent studies have initiated steroid treatment as an interdictive therapy for infants who were considered to be at high risk of developing BPD.

2.1. Corticosteroids in evolving BPD. Corticosteroids administered systemically in the first weeks of life to infants at risk of or with CLDI improve respiratory status, and result in faster weaning from the ventilator (302, 431–433). The most appropriate timing of commencement of such treatment, particularly very early administration (less than 48 hours of age), remains controversial (433–436) and under investigation. It has been proposed that the results of corticosteroid treatment vary with the age at which treatment is initiated. Steroids started within the first 96 hours of life (early therapy) or between 7 and 14 days of age (moderately early therapy) facilitate weaning from the ventilator, can decrease death or BPD at 28 days postnatal age and 36 weeks postconceptional age, and decrease a later need for "rescue" steroids for BPD (437–439). Early steroid administration also reduces the incidence of BPD in very low birth weight infants who received surfactant (436). However, such early and moderately early therapy has been associated with an increased incidence of hyperglycemia, hypertension, gastrointestinal bleeding, isolated intestinal perforation, decreased growth, and nosocomial infection. Late therapy (treatment after 3 weeks of age) facilitates extubation by 28 days after initiation of treatment, but is associated with hypertension and poor growth. The risks vary with the treatment plan. Adrenal and hypothalamic–pituitary axis suppression have also been described (440, 441). There are also concerns regarding the delayed side effects of prolonged corticosteroid use in infancy. There are data that early treatment with steroids may result in decreased alveolar number (442). Adverse neurologic outcomes have been described, including abnormal neurologic examinations, cerebral palsy, and developmental delay (254–256). Cardiac complications, including fatal cardiomyopathy and interventricular septal hypertrophy, have also been described (443). Metaanalyses have reviewed the effectiveness of postnatal corticosteroids in the prevention of BPD (444–446). The National Institute of Child Health and Human Development multicenter trial suggests that, in view of the associated side effects and lack of long-term benefit, routine use of oral corticosteroids is discouraged (447).

As a consequence of concern regarding the side effects of systemic steroids, attention has turned to examining the efficacy of steroids given topically. Nebulized beclomethasone given over 4 weeks improved lung function (448); but such solutions are acidic and their administration has, in certain infants, been associated with a paradoxical reduction in lung function (449). Beclomethasone has also been given via an MDI as 1 mg/kg per day in three divided doses. Using such a regimen for 7 days resulted in, compared with placebo, a significantly greater proportion of infants being extubated during the study period (450). This advantageous effect was not, however, replicated with budesonide, although significant improvements in oxygenation and a reduction in ventilatory requirements were noted (451). Although topical treatment may avoid the side effects associated with systemic administration, a randomized trial (452) has demonstrated that any beneficial effect may occur more slowly. Improvements in lung function were seen only after 7 days and not 36 hours, as with systemic treatment (452).

Inhaled steroids begun before 2 weeks of age and given for 4 weeks to ventilator-dependent preterm infants can reduce the need for mechanical ventilation and "rescue" systemic glucocorticosteroids, but have not been shown to reduce the incidence of BPD (453, 454). A Cochrane database analysis concluded that 1–4 weeks of inhaled steroids facilitates extubation in intubated infants with BPD without increasing the risk of sepsis (455).

2.2. Corticosteroids in established CLDI. Antiinflammatory drugs have been used to ameliorate asthma-like symptoms in infants with CLDI. There are few studies documenting their efficacy, however. Antiinflammatory agents given regularly to prematurely born infants symptomatic at follow-up with CLDI reduce symptoms, improve lung function, and lessen the need for bronchodilator therapy. Corticosteroids (456) given via an MDI and spacer have been used successfully, even in patients aged less than 1 year. This is the preferred route for preventing side effects of systemic corticosteroids. The more recent approval in the United States of nebulized budesonide for use in infants has made this an option as well. As in infants with asthma, infants and children with CLDI treated with inhaled corticosteroids should be monitored for potential steroid side effects, including delayed growth, increased blood pressure, osteoporosis, adrenal suppression, and cataracts. These side effects are seen much less frequently than with systemic corticosteroids. Oral candidiasis is a problem, however, and can be easily avoided by rinsing the child's mouth after inhaled corticosteroid use. This is most readily accomplished by timing the use of inhaled corticosteroids to occur just before tooth brushing twice a day.

2.3. Other antiinflammatory agents. Limited experience with cromolyn has been reported. A prospective randomized controlled trial found that initiation of cromolyn in intubated infants

with RDS did not reduce the incidence or severity of BPD defined as oxygen dependence at 30 days of life (457). A retrospective study that treated infants with established CLDI reported that cromolyn improved pulmonary function and reduced ventilatory requirements in some patients (458). Nedocromil sodium (459) and sodium cromoglycate (460) have also been administered by MDI, spacer, and face mask.

Although leukotrienes have been implicated in the pathogenesis of CLDI and increased levels have been reported in bronchoalveolar lavage fluid from these infants (*see* Section II.A.1: LUNGS), there have been no studies to date on the use of leukotriene modifiers in infants with CLDI. It is, however, reasonable to consider their use in children over 2 years of age with a prominent asthmatic component.

3. Oxygen therapy. Young patients with CLDI often have oxygen desaturation in room air. Physiologic consequences include bronchospasm (150, 151) and pulmonary hypertension with secondary right-to-left shunting at the atrial level. Hypoxemic infants lack energy to feed, learn, and they sleep more than their peers. Furthermore, infants with CLDI are known to function at an increased metabolic rate that is not ameliorated solely by improving pulmonary mechanics (461).

Although a compelling body of evidence supports the use of chronic supplemental oxygen (391, 462), it is administered for this group of infants somewhat reluctantly. This is largely a result of perceived consequences of oxygen toxicity to the eye and the lung. In addition, some have difficulty seeing the child as "oxygen dependent" and are therefore reluctant to provide the needed supplementation. Data from a study assessing the effects of differing levels of oxygen supplementation (targets of 89–94 and 96–99% oxygen saturation) on retinal development suggested that pulmonary exacerbations of chronic lung disease were greater in the group with the higher saturation target (463). Increasingly, however, oxygen is viewed as a safe and relatively convenient means for maximizing growth and development.

3.1. Physiologic effects of enhancing oxygenation. Convincing data support normalization of arterial oxygen levels utilizing supplemental oxygen in adult patients with chronic pulmonary disease for both survival and function (464, 465). In infants, direct measurement of pulmonary arterial pressure, pulmonary arterial resistance, and oxygen saturation clearly demonstrates that physiologic levels of oxygen saturation significantly lessen the risk of pulmonary hypertension (152, 358). Longer term clinical observations support this view, albeit controlled studies have not been performed. In addition, long-term observations support an enhanced nutritional and behavioral state in the well-oxygenated child (466).

Alveolar hypoxia produces not only pulmonary vasoconstriction but also airway constriction that can contribute to hypoxemic episodes (150, 151). Oxygen reduces the level of pulmonary artery pressure, occasionally to the normal range (358, 359). However, pulmonary pressure in patients with severe CLDI may not normalize because of structural remodeling of the vascular bed (152, 206, 354, 355, 359, 467). Oxygen can acutely reverse the functional hypoxic vasoconstrictive component but not the restrictive, structural aspect of pulmonary hypertension. The goal of oxygen therapy is threefold: to promote growth and therefore repair of the developing lung, to provide adequate exercise tolerance, and to diminish pulmonary artery hypertension and right ventricular work load. The ideal oxygen saturation satisfying these criteria is located on the flat portion of the oxygen–hemoglobin dissociation curve, so that a small decrease in the partial pressure of oxygen does not produce a large reduction in oxygen saturation, and is not too elevated to reduce the hypoxic respiratory drive in patients who retain carbon dioxide. An oxygen saturation between 90 and 95% fulfills these requirements (468); values in the higher portion of this range provide more of a safeguard against transient decreases in oxygenation. Catheterization studies in patients with CLDI have documented an inverse relationship between oxygenation level and both pulmonary pressure and pulmonary vascular resistance (152, 196, 206, 351, 354–356, 358, 359, 362, 467). The pulmonary pressure reaches its lowest value when the systemic oxygen saturation exceeds 95% (152, 358). Oxygen saturations in this range can be achieved in some patients with nasal cannula oxygen (flow rate, 0.25 to 3 L/min) with pulmonary artery pressure reductions similar to that observed with the use of oxygen administered via a hood with $F_{I_{O_2}}$ greater than 0.80 (152, 359). Delivering oxygen via a nasal cannula instead of a mask or hood, especially during feeding and handling, provides more consistent oxygenation and improved growth (391, 466, 469, 470). Maintaining systemic oxygen saturation greater than 90% also reduces the frequency of central apnea (147) and the transient elevations in pulmonary artery pressure associated with alveolar hypoxia. In addition, because patients with CLDI have an abnormal response to hypoxia following arousal that can lead to prolonged apnea and bradycardia, maintaining the oxygen saturation between 90 and 95% may decrease the higher incidence of sudden infant death in this patient group (169, 174). Oxygenation varies with activity and decreases with feeding (145, 471) or during sleep (145, 147, 148) so that monitoring during awake, feeding, and sleeping periods is important before weaning a patient from supplemental oxygen. Persistent use of night-time oxygen is often necessary after day-time use has been discontinued because of altered lung mechanics and irregular breathing during sleep (145, 148). The mean corrected age when supplemental oxygen was discontinued in a study from Denver was 7.9 months (353). The mean duration of low-flow oxygen therapy in studies at sea level (Toronto, Baltimore) was 3.5 to 4.5 months (391, 472). If there is persistent right ventricular hypertrophy or a slow wean from supplemental oxygen, patients should be screened for undertreatment (especially during sleep) or poor compliance with oxygen (207, 466), and other conditions such as unsuspected congenital cardiac defects (355, 356), upper airway obstruction from enlarged tonsils and adenoids or subglottic cyst (356), and chronic aspiration with gastroesophageal reflux (207, 473). In this situation repeat echocardiography, bronchoscopy, monitoring of respiratory pattern and degree of oxygenation during sleep, or esophageal pH probe may be necessary.

3.2. Assessment of oxygen level. Sufficient evidence exists to accept oxygen saturation measurement as determined by pulse oximetry as the primary guideline (474, 475), even in the presence of carbon dioxide retention (476, 477). Multiple determinations are made in various states including rest, sleep, feeding, and high activity, and in various positions. Furthermore, arterial blood gas, end-tidal CO_2, or bicarbonate determination can be helpful in infants with suspected carbon dioxide retention, although the latter two are more useful when done serially. An echocardiogram and ECG are helpful when relatively severe pulmonary hypertension is suspected. Continuous oxygen saturation monitoring at home, monitoring oximetry during activity or during feeding, and, if necessary, polysomnography are helpful, particularly for infants who are not doing well (349).

3.3. Recommendations for saturation level. (*See* flow sheet, Figure 4, and Section IV.B.9: OPHTHALMOLOGY.) Higher oxygen saturation levels prevent most desaturation (146). Cardiac catheterization in relatively few and severely affected infants has demonstrated that pulmonary arterial pressure is lower at high levels of saturation (152, 358). Unfortunately, longitudinal, controlled studies comparing progress at various levels are not available. On the basis of observations regarding pulmonary hypertension, prevention of intermittent hypoxemia, and the knowledge that

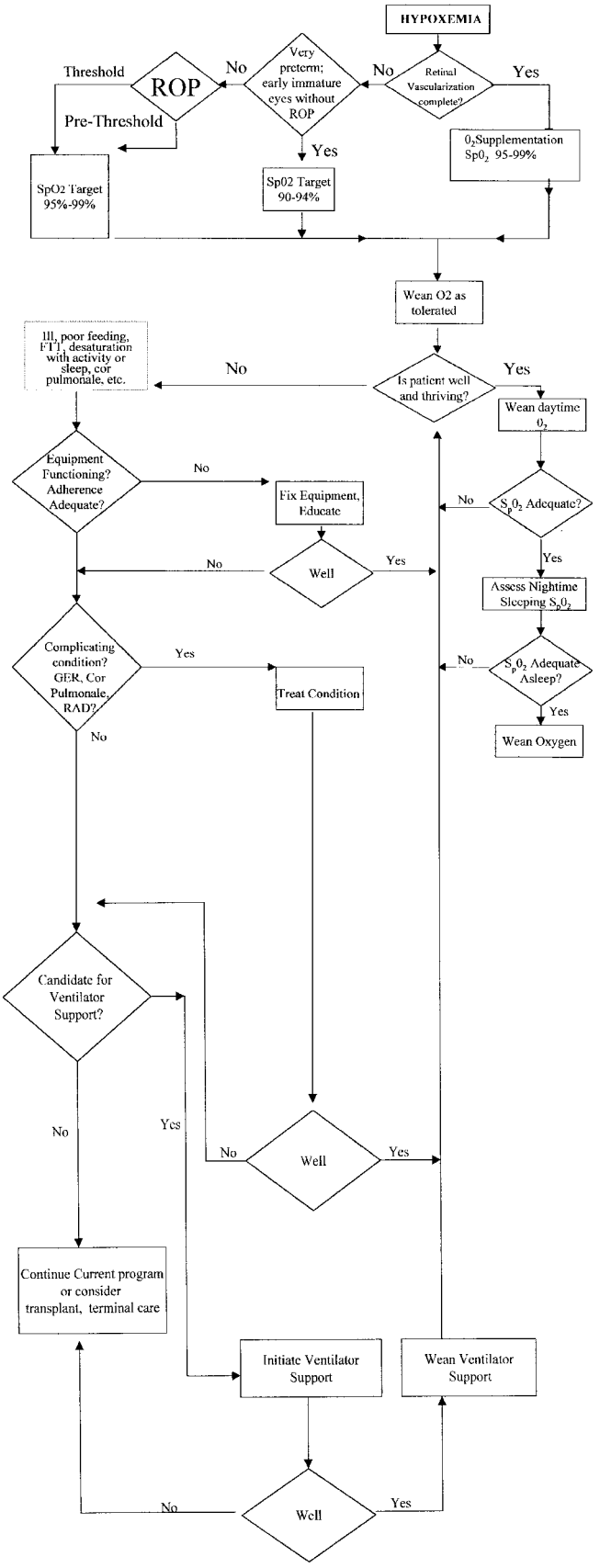

Figure 4. Oxygen supplementation and ventilator support decision tree for infants with CLDI. FTT = failure to thrive; GER = gastroesophageal reflux; RAD = reactive airway disease; ROP = retinopathy of prematurity; Sp_{O_2} = oxygen saturation of arterial blood as determined from a pulse oximeter.

95–100% represents the physiologic range of oxygen saturation for this age (478, 479), we recommend the provision of supplemental oxygen sufficient to achieve a saturation of 95% or more once passed the age of oxygen-induced retinopathy (480, 481). This provides a "buffer" zone against oxygen desaturation that targets of 90% or more do not. Bearing in mind the cautionary notes sounded by the STOP-ROP (Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity) trial (463) and the preliminary report of the BOOST (Benefits of Oxygen Saturation Targeting) trial (482) on the increased number of exacerbations of CLDI seen in the infants targeted for saturations of 95% or more, compared with the 89–94% range, it might be best to aim for the lower end of the 95–99% range while awaiting the result of further studies. However, it is important to remember that these trials compared saturation targets applied to very preterm infants early in their course. Higher targets applied to postterm, postconceptional age infants after the nursery course are likely safe and effective in promoting growth and preventing pulmonary artery hypertension. These recommendations are similar to others (483). Recommendations for targeted oxygen saturation while still in the age range of potential oxygen-induced retinopathy are more controversial (*see* Section IV.B.9: Ophthalmology). Figure 4 presents a suggested approach.

3.4. Techniques for long-term oxygen administration.

Nasal Cannula. The nasal cannula is the most widely used device for the delivery of enhanced FI_{O_2}, particularly in the ambulatory setting. It is convenient, safe, and well tolerated. Many nurseries utilize a system to blend oxygen with room air in an attempt to provide a relatively precise FI_{O_2} because relatively small changes in flow rates may produce unpredictable changes in FI_{O_2} (484). Refined calculations have been suggested to lend a further degree of precision to the determination of FI_{O_2} (485). Although calculations for determining FI_{O_2} have been suggested as a practical matter these are not needed. In the ambulatory setting most clinicians provide low-flow 100% oxygen to reach a predetermined oxygen saturation reading. This is easily adjusted by the parents to match specific levels of activity. Feedback devices that automatically adjust to variations of saturation are under investigation (486, 487). Nasal anatomy, presence of mucus, and the like contribute to the flow of oxygen required to maintain a specific level of saturation. In some cases, nasopharyngeal oxygen administration can be used, but its potential adverse effects on swallowing function make its use less optimal than nasal cannulas. Most centers advocate humidification of oxygen (488) although studies of the efficacy of nonheated humidification are lacking.

Oxygen via Tracheotomy. The tracheostomy collar is most widely used. Some have proposed a modification to keep the size and appearance minimal (489). Most advocate enhanced humidification. There is limited experience with transtracheal oxygen administration in childhood (490).

Face Tents and Head Hoods. Although an acceptable method of delivery of enhanced oxygen and humidity, they present several problems that complicate widespread usage. They limit mobility and visibility of the patient. Carbon dioxide can build up in the face of insufficient flow rates. Temperature and moisture buildup can be a problem.

Oxygen Delivery Systems. The selection of an appropriate delivery system depends on the flow and concentration of oxygen needed (491). Consideration of equipment availability on the part of local vendors and insurance coverage is considered. Options include compressed gas, liquid oxygen, and concentrators.

3.5. Traveling with oxygen. At sea level, considerations relate to convenience, portability, and reliability. Both gas and liquid tanks are suitable for the task. The major considerations relate to safely securing the oxygen source, assuring a sufficient supply,

and confirming the ability to observe and monitor the infant during travel.

Vacationing at altitude and airline travel raise the added consideration of a decreased inspired oxygen concentration. Commercial aircraft generally maintain cabin altitudes between 6,000 and 8,000 ft, with the newest generation of aircraft utilizing the higher altitudes. Furthermore, brief excursions to somewhat higher levels are allowed during special circumstances. Without supplemental oxygen, an altitude of 8,000 ft produces an inspired P_{O_2} of 118 mm Hg as opposed to 159 mm Hg at sea level (492). Therefore, a patient with marginal pulmonary reserves or who is maintained on supplemental oxygen will require an enhanced $F_{I_{O_2}}$. One method to estimate this is as follows (493):

$$F_{I_{O_2}} \times (BP - 47)\ [\text{ground level}] = F_{I_{O_2}} \times (BP - 47)\ [\text{altitude}]$$

where BP is barometric pressure in millimeters of mercury and $F_{I_{O_2}}$ is fractional inspired concentration of oxygen. It will be necessary to estimate the $F_{I_{O_2}}$ from the flow rate. Hypoxic challenges in the pulmonary function laboratory can also be performed to predict the effect of airline travel on Sa_{O_2} in a given patient. An inspired oxygen concentration of 15–16% will mimic the inspired P_{O_2} in a commercial aircraft.

It is best to have the family contact the airline well in advance of the flight to explain the child's oxygen requirements. An attempt should be made to utilize direct flights. If not, arrangements should be made to have oxygen available between flights for oxygen-dependent infants. The physician will then have to prescribe the amount and duration of oxygen therapy and will most likely be requested to certify that the patient may fly safely. Generally the airlines provide useful information.

3.6. Monitoring the oxygen-dependent infant in the home. Vigilance for an empty oxygen supply, dislodged cannula, or blocked valve is paramount. Knowing the pulmonary reserve on room air is helpful, especially during sleep when the supplemental oxygen requirement may increase. In general, potentially unstable patients are provided with an alarm system usually consisting of a cardiopulmonary monitor. Oximetry has the advantage of providing an earlier warning but movement artifact remains a problem. However, an oximeter in the home has the additional advantage of providing the caretaker with useful information, thus saving on the expense and time for office or hospital visits. This is particularly true during times of illness, when home oximetry reports from the parents can help determine whether the supplemental oxygen flow rate or concentration should be increased, or whether the child needs to be further evaluated in the office or emergency room. Insurance providers may support use of these devices in the home. In addition, home care providers also will take readings in the field.

3.7. Weaning from supplemental oxygen. (*See* flow chart, Figure 4.) Weaning is accomplished by obtaining oxygen saturation measurements on progressively decreasing oxygen levels. This is best done by continuous oxygen saturation monitoring during sleep. With current technology and qualified home observers, it is now possible to do such studies in the home (494–498), but this should be done only in children without concomitant signs of obstructive sleep apnea. Making decisions about weaning based on short (20–30 minutes) awake oximetry studies is not advisable; such studies can be misleading. One- to 2-hour studies perform better as predictors of ability to wean (499, 500). If high saturation targets (greater than 97%) are maintained while awake, this is a good indication of the ability to maintain oxygen saturations of greater than 92% while asleep (499). Finally, one must be cognizant of the differing requirements during activity and sleep. In addition, an initially excellent reading does not ensure that saturations will not drop several hours and even days later. Therefore, it may be helpful to perform block weaning (hours off) toward the end of the weaning process. The families should be counseled that respiratory infections often result in the infant being administered supplemental oxygen once again.

3.8. The child who is not doing well while receiving supplemental oxygen. The following should be considered if a patient is not doing well during oxygen supplementation (*see* flow sheet, Figure 4):

- Another or an additional medical diagnosis
- Not getting the oxygen—nonadherence
- Supply has run out
- Blocked tube or valve
- Unnoticed dislodgment of cannula
- Condition increasing in severity—frequently after a respiratory illness
- Pulmonary hypertension with atrial level right-to-left shunting

4. Airway problems and tracheostomy care. Surgical treatment of laryngeal or glottic webs, cysts, or granulation tissue is often curative. When subglottic stenosis is severe, an anterior cricoid split may allow for widening of the subglottic space and allow for healing without the need for tracheostomy tube placement (501). If the anterior cricoid split fails to relieve obstruction, or if the infant does not meet criteria for the procedure, tracheotomy is necessary to bypass the obstruction. Tracheostomy tube placement should be undertaken when other means of correcting the obstruction have been ruled out, because speech development will be delayed and the need for specialized care and monitoring will be increased. A tracheostomy allows for gradual surgical correction of subglottic stenosis by a variety of techniques, including laryngotracheal reconstruction. Guidelines on the care of the child with chronic tracheostomy have been published (502).

Tracheostomy tube placement alone or in conjunction with prolonged continuous positive airway pressure has also been advocated for the treatment of tracheomalacia (119, 134, 503–507). Presumably, the collapsible airway segment should reside within the length of tracheostomy tube for this approach to be effective without the concomitant use of distending pressure. The use of elongated tracheostomy tubes has been advocated to allow for stenting of the distal trachea (503).

Relief of fixed airway obstruction can be achieved by open tube resection of granulation tissue (115–117, 119, 120). Distal tracheal and bronchial stenoses have been corrected by balloon dilation under direct visualization (117, 119, 508) or fluoroscopic guidance (509), or by electroresection (119).

Use of α-adrenergic agents such as racemic epinephrine may afford temporary relief for patients with mild to moderate subglottic stenosis who experience acute exacerbation of symptoms with upper respiratory tract infections. In this setting, pharmacotherapy is aimed at reducing any edema superimposed on the already narrowed airway and unloading the nasal airway to minimize the resistive pressure losses leading to excessively negative pressures at the level of the glottis. Systemic corticosteroids have been used early in the course of subglottic stenosis, but their effectiveness has not been formally assessed.

Several case reports of infants and children with intrathoracic tracheomalacia describe relief of symptoms after aortopexy or application of external tracheal splints (119, 510). More recently, distal tracheomalacia and bronchomalacia have been successfully treated by implantation of expandable intralumenal metallic stents (511). Most of these series involve children with congenital airway problems, so that data regarding efficacy of these procedures in children with CLDI are extremely limited. The need to resort to their use is extremely rare.

Airways can be made stiffer by increasing airway smooth

muscle tone (512–515). When the major cause of obstruction results from a collapsible trachea, use of bronchoconstrictor agents can relieve obstruction and improve forced expiratory flows (346). Conversely, if dynamic airway collapse occurs because of reversible small airway obstruction, bronchodilator administration will relieve small airway obstruction and lessen expiratory pressure effort. This in turn can decrease dynamic airway collapse. However, if bronchodilator drugs are administered in the setting of fixed small airway obstruction, they cause relaxation of central airway smooth muscle without decreasing expiratory pressure effort. This can exacerbate dynamic airway collapse and worsen obstruction (346). Often, the only way to tell whether bronchodilators will improve or worsen airflow obstruction in the clinical setting is to perform pulmonary function testing before and after their administration.

5. Long-term ventilator care. Chronic mechanical ventilation in a long-term facility or home setting is occasionally required in infants with severe CLDI. This usually occurs under two circumstances: (*1*) infants with severe lung disease and chronic respiratory failure who have never been able to be weaned from the ventilator in the NICU, and (*2*) infants who have been weaned from the ventilator, but have suffered a setback severe enough to warrant reinstitution of mechanical ventilation. Home mechanical ventilation requires a major commitment of time, money, and resources by health care workers and family members alike, but it can be life saving. Guidelines for the accomplishment of home mechanical ventilation have been published (516–518).

6. Diuretics, afterload reducers, and other cardiac pharmacology. Diuretics are often used to treat infants with CLDI. Treatment with furosemide (238, 239, 519) or with chlorothiazide and spironolactone (274, 275, 520) has been shown to improve pulmonary function by increasing dynamic pulmonary compliance, increasing specific airway conductance, and decreasing airway resistance. The most commonly used diuretics in infants with CLDI are chlorothiazide, furosemide, and spironolactone (521). The sites of action differ, and therefore they are often used in combination. Chlorothiazide inhibits sodium and chloride reabsorption in the distal tubule, furosemide inhibits sodium and chloride reabsorption in the ascending limb of the loop of Henle, and spironolactone decreases the activity of the sodium potassium pump in the distal tubule, decreasing sodium resorption and potassium excretion. Thiazide absorption from the gastrointestinal tract is efficient, onset of action is within 1–2 hours, and drug is cleared within 3–6 hours. Furosemide is also efficiently absorbed, with an oral onset of action of 1 hour and an intravenous onset within minutes. Pharmacokinetic differences between adults and children, such as reduced clearance and prolonged half-life, exist for furosemide, and little is known about the timetable of maturation of these differences (522).

Clinical toxicity of chlorothiazide is rare. Side effects of furosemide include hypercalciuria, and this has led to nephrocalcinosis (523). Transient deafness is rare, but it is best to avoid furosemide when using other ototoxic drugs such as aminoglycosides. The thiazide and loop diuretics can cause hypokalemia and metabolic alkalosis, which in turn can exacerbate CO_2 retention in patients with CLDI. This is best prevented, and treated if present, with adequate KCl supplementation. On the other hand, spironolactone can cause hyperkalemia, especially when not used in combination with other diuretics or when used concomitantly with potassium supplementation. Periodic monitoring of serum electrolytes is therefore essential in infants and children treated with chronic diuretic therapy.

Despite their widespread use, little is known about the effects of long-term use of diuretic therapy in infants with developing or established CLDI with regard to survival, duration of ventilatory support or oxygen administration, potential complications, and long-term outcome (524–526). Although inhaled diuretics may transiently improve lung function, they have not been shown to have a role in the chronic management of CLDI (527, 528).

The use of intravenous, oral, or inhalational vasodilators other than oxygen should be considered experimental and limited to research protocols. The testing of these agents requires careful hemodynamic monitoring with intravascular catheters in a hospital setting. The basis for considering the use of such agents is the relaxation of vasomotor tone associated with medial hypertrophy of the pulmonary arteries and the possibility of reducing the amount of supplemental oxygen that is necessary to lower pulmonary pressure (196). There are a limited number of reports on the use of nifedipine (206, 529), diltiazem (530), hydralazine (358, 531), or prostacyclin (196) that have been largely limited to acute drug testing. All these agents are nonselective vasodilators and can cause systemic hypotension, tachycardia, and hypoxemia due to ventilation–perfusion mismatching. In patients with large systemic-to-pulmonary collateral vessels hypoxemia can also result from decreased perfusion to the lung caused by a reduction in systemic vascular resistance (358). The calcium channel-blocking agents also can have a negative inotropic effect. There is limited information about the pharmacokinetics of these agents in infants, the short- and long-term effects in this age group, and the persistence of beneficial effects with oral use. There have been preliminary reports on the use of inhaled nitric oxide as adjuvant therapy in children with CLDI who have severe hypoxemic respiratory failure (532, 533). This agent is a selective pulmonary vasodilator that improves oxygenation and lowers pulmonary vascular resistance without systemic hemodynamic effects. Additional studies are necessary to monitor potential side effects, determine the minimum effective acute dose, and the role of prolonged low-dose nitric oxide therapy.

Although most infants with CLDI outgrow systemic hypertension, sustained elevations of blood pressure should be treated. Acute elevations in blood pressure can occur with rare reports of cerebrovascular accidents (208). Electrocardiographic evidence for left ventricular hypertrophy is present in approximately one-fourth of the hypertensive infants (208). If systemic steroids are being administered, such medication should be tapered because this can result in resolution of hypertrophy (211). Pharmacologic agents used have included hydrochlorothiazide, spironolactone, furosemide, propranolol, or hydralazine (208). The mean duration of therapy for systemic hypertension is 7.7 months (range, 2 to 11 months).

7. Nutrition. Optimizing growth and development remains the principal goal of nutritional support of infants with CLDI (534). Initially many of these patients will be supported by parenteral nutrition or by a combination of parenteral and enteral nutrition, particularly while they are supported by mechanical ventilation. The optimal techniques and composition of enteral feedings remain the subject of research studies. However, in general the infants will require (*1*) increased energy compared with the needs of healthy age-matched infants; (*2*) special attention to suck and swallowing coordination and gastroesophageal reflux; (*3*) oxygen supplementation to meet their needs for oxygen that result from increased metabolic rates, in a setting of diminished ability to transfer oxygen from the atmosphere to the circulation. Anecdotal experience suggests that maintaining oxygen saturation above 95% helps keep pulmonary vascular resistance low, which diminishes right heart "strain," thereby decreasing energy requirements; and (*4*) fluid restriction in infants in whom diuretic therapy is insufficient to avoid pulmonary edema.

7.1. Formulas. Specially designed formulas are available to meet the extra calorie, protein, calcium, phosphorus, vitamin,

and mineral needs of the acutely ill and chronically ill infant with CLDI. Nutrient requirements are often complicated by fluid restriction and the use of diuretics and other medications, which cause nutrient loss or catabolism. Breast milk alone and standard infant formulas are unable to meet the increased needs. These higher nutrient requirements can be met through the use of breast milk combined with breast milk fortifier, preterm formulas, and preterm follow-up formulas as the infant grows older.

Because of high caloric needs, 24 kcal/oz for newly born infants is usually suggested with a change to 30 kcal/oz or more for infants nearing 1 year of age and toddlers. Slow transition to these calorically dense formulas should improve tolerance.

Because of the higher energy requirements of these infants, an initial start with 120 kcal/kg per day often will result in "catch-up" weight gain. If weight does not respond, the following equation will provide guidelines for calories for "catch-up" weight gain: kcal/kg per day = (Recommended Dietary Allowance for chronological age in kcal/kg multiplied by ideal weight for height) divided by actual weight (535).

To increase formulas above 24 kcal/oz for the infant less than 1 year of age, modules in the form of fat or carbohydrate may be used. Fat, as long- or medium-chain triglygerides, and carbohydrate, as glucose polymers, can be added as modules to the formulas to increase the caloric density beyond 24 kcal/oz and meet energy needs of 150 kcal/kg/day or more (536). Providing more energy from fat may help to reduce the CO_2 production rate, although the benefits of increased dietary fat over the long term remain to be demonstrated. Adding extra fat may decrease gastric emptying, thus contributing to gastroesophageal reflux and may lead to ketosis. Stools can be tested qualitatively and quantitatively for fat in an infant with loose, greasy stools and poor growth. Stools from infants receiving formulas with added carbohydrate should be observed and if frequent and watery should be tested for reducing substances. If abnormal stools occur, then the amount of fat or carbohydrate added to the formula should be reduced. When concentrating formula and adding modules to increase calories, macronutrients should be well balanced: 8–12% protein, 40–50% carbohydrate, and 40–50% fat (383). Caloric density of formula may also be increased by adding rice cereal: 1 teaspoon of rice cereal per ounce of formula increases caloric density by 5 kcal/oz. Blended avocado, which also adds potassium to the diet, may also be used to increase the caloric density.

The use of fat or glucose to support the energy needs of infants with CLDI also remains the subject of investigation. The increased CO_2 production from metabolism of carbohydrates compared with fats has led some to increase the amount of fat in infant formula or intravenous solutions, such that the majority of calories delivered are from fat (537, 538). Infants with CLDI fed a formula in which fat contributed 67% of calories had lower rates of CO_2 production and lower respiratory quotients than those fed a formula with a lower fat, higher carbohydrate content. However, pulmonary function test results were equivalent in both groups of infants and both formulas promoted adequate growth and weight gain over the short-term study (539).

Protein intake should be at a level similar to that of a healthy, growing infant of a similar age. It should be recognized that protein catabolism induced by corticosteroid medications can be significant. However, it is uncertain how much "extra" protein should be provided to compensate for losses when corticosteroids are used or even if it is possible to overcome the catabolic process (540). These requirements range from 3 g/kg/day in early infancy to a rate of about 1.2 g/kg/day in early childhood. The young infant should receive no more than 4 g/kg/day because of the risk of acidosis related to immature kidneys.

Assessment of micronutrients, in addition to macronutrient balance, is necessary. Oral and enteral feed intake may be low in vitamins and minerals, and supplementation should be considered if they are less than 100% of the Recommended Dietary Allowance. A standard multivitamin (0.5–1.0 cm^3) should be adequate.

Vitamin A supplementation to the level of 1,500 to 2,800 IU/kg/day or 450 to 840 μg/kg/day in infants appears to be safe and has led to a decreased incidence of bronchopulmonary dysplasia in infants who are vitamin A deficient with respiratory distress syndrome, a decreased number of days during which these infants were provided with mechanical ventilation and supplemental oxygen, and a decreased number of days in an intensive care unit setting (541). In contrast, others have found no beneficial effect of vitamin A supplementation if the infant is vitamin A sufficient at the time of diagnosis (542). It may be that the inconsistent results are a result of dosing regimens. One trial showed a modest effect of high-dose vitamin A in preventing CLDI (543).

Fluid intake may need to be restricted. In practice, it is often difficult to reconcile the need to provide adequate calories for growth and at the same time severely restrict fluid intake. Smaller, immature infants receiving 24–28 kcal/oz formula may need to start with 75–90 cm^3 fluid/kg/day. From 95 to 150 cm^3 fluid/kg/day may be well tolerated later as lung health improves (534).

Renal solute load and osmolality should be considered when concentrating formula and adding modules. Providing enough free water is important and should be frequently monitored. The American Academy of Pediatrics recommends that infant formulas have an osmolality of less than 450 mOsm/L. Medications and carbohydrate modules can increase osmolality.

7.2. Feeding techniques. Continuous naso- or orogastric tube feedings lower resting energy expenditure and are almost universally necessary in young, immature infants with CLDI. As respiratory status improves bolus feedings may be initiated; however, additional supplemental oxygen may be required. If adequate calories for growth cannot be taken during the day, the use of continuous nighttime gavage feedings may greatly supplement caloric intake, but the infant must be monitored for evidence of aspiration. Suck and swallowing dyscoordination or weak swallowing limits the use of bottle or breast feeding initially (471). Concomitant stimulation of oral–motor skills should occur in all tube-fed patients to prepare them for eventual feeding by mouth when there is no longer a risk of oral–pharyngeal aspiration and swallowing functions have matured (544).

Whether feeding by gavage, nippling formula, or expressed human milk, or feeding directly at breast, the infant's behavioral state and neuroregulatory system should be taken into account. These babies are easily overwhelmed by tactile, visual, auditory, and kinesthetic stimuli. When gavage fed, they should remain in their shielded isolette, supported gently and given the opportunity to suck on a pacifier. Feeding should be timed to coordinate with the baby's natural sleep cycle to encourage a natural pattern between sleep, awake time, and feeding. Excessive crying periods should not occur because of a predetermined feeding schedule.

Oral–motor dysfunction during feeding should be recognized as soon as possible. A skilled nurse or occupational therapist may be helpful in the diagnosis and management of this condition. Parents should be informed about appropriate maneuvers to improve neuromuscular coordination during feeding such as thickened feeds. Supervised practice before discharge is useful.

Parents of an infant with CLDI are usually anxious about weight gain as a marker of the baby's improving health. Because weight gain is often slow and setbacks are common, it is important to provide parents with realistic expectations about growth. This is especially critical when the baby is taken home and the

parents now have primary responsibility for feeding and weight gain.

7.3. Electrolytes and mineral homeostasis. Electrolyte requirements from the end of the first month of life onward are in the range of 4 to 7 mEq/kg/day (sodium) and 2–4 mEq/kg/day (potassium), but must be monitored and provided to support the actual clinical conditions of each infant (545). The use of diuretics to manage fluid requirements and dexamethasone to accelerate lung maturation may often complicate the management of appropriate electrolyte and mineral homeostasis in these infants. Calcium and phosphorus intakes for parenterally fed preterm infants with a body weight of 1–3 kg are as follows: calcium, 60–90 mg/kg/day (1.5–2.25 mmol/kg/day); phosphorus, 47–70 mg/kg/day (1.5–2.25 mmol/kg/day); and magnesium, 4.3–7.2 mg/kg/day (0.18–0.30 mmol/kg/day). Enteral intakes are as follows: calcium, 120–230 mg/kg/day (3.0–5.63 mmol/kg/day); phosphorus, 60–140 mg/kg/day (1.94–4.52 mmol/kg/day); and magnesium, 7.9–15 mg/kg/day (0.33–0.63 mmol/kg/day). A randomized blinded nutrition study of 60 infants with CLDI showed greater "catch-up" linear growth and improved lean body and bone mass when the infants were fed a formula that had a high protein, calcium, phosphorus, and zinc content (546). After a weight of 3.0 kg is achieved mineral intakes similar to that of term infants are recommended. Vitamin D intakes range from 40–160 IU/kg per day for preterm infants to 150–400 IU/kg/day to a maximum of 800 IU/kg/day for term infants with adequate mineral intake (547).

The infant who is receiving human milk or fortified human milk may need iron supplementation of 2–3 mg/kg per day. Premature infant formulas contain iron and additional iron should not be given unless iron deficiency is diagnosed (536).

Infants should be monitored by repeated assessment of their micro- and macronutrient intakes and adjustments made to meet their requirements. Minimal supplements may be necessary, particularly if fluid is severely restricted or the patient is receiving diuretics. Weight, length (or height), and head circumference should be measured serially as well to determine the adequacy of nutritional support.

7.4. Gastroesophageal reflux. Pathologic gastroesophageal reflux is a significant problem for infants and young children with CLDI (118). When diagnosed, medical management with antacids, H-2 receptor antagonists, or proton pump inhibitors and/or prokinetic agents is often successful in reversing the pathologic symptoms. When symptoms are life-threatening or persistent then a fundoplication may be indicated.

8. Developmental intervention. On the basis of sound neurodevelopmental principles, recommendations for care in the nursery and afterward can be made to enhance outcome.

8.1. Procedures. Procedures such as bathing, change of clothes, venipuncture, suctioning, and lumbar puncture can be coordinated with the goal to prevent overstimulation and excessive energy consumption. Nursing personnel can plan procedures at moments when a baby shows behaviors that indicate a readiness to interact.

Sponge bathing may initiate a tactile overload in these fragile babies. Alternatively, immersion in a warm bath has a soothing effect. An opportunity for sucking and holding onto the caregiver's finger during a procedure encourages a relaxed state. Limiting unnecessary stimulation such as stroking, talking, and position shifts should be encouraged. Sleep cycles should be monitored and the interruption of deep sleep prevented whenever possible. The maintenance of a calm environment and schedule with gradual transitions when initiating a procedure will preserve energy for the critical time of feeding and interpersonal interactions (548).

8.2. Attachment. To maximize interpersonal experiences and encourage attachment behaviors, NICU caregivers should be consistent from shift to shift. When feasible, a small cluster of caregivers will not only enhance the baby's development but also will be helpful to the family.

Social interchange with an infant with CLDI should be modulated and carefully titrated. Facial expressions that are not overly animated but quiet looking, and firm containment of the limbs and trunk set the stage for the optimal maintenance of an alert state. Talking should be limited while looking at the baby so that all the infant's reserve can be used to visually engage the caretaker.

8.3. Physical environment. In the NICU and at home, the physical environment that surrounds a child with CLDI can be organized in a way to minimize the negative effects of the disease process. The infant's crib or isolette can be placed away from sinks, telephones, and radios to avoid excessive auditory stimulation. Where possible, excessive activities of NICU personnel near the infant should be limited. Lighting can be adjusted by dimming when critical observation and monitoring are no longer necessary. The infant's clothing can aid in state regulation and encourage sleep or a quiet alert state by swaddling and a hat. The maintenance of a safe, quiet environment that limits sensory overload prepares the child for social interaction and preserves its energy for feeding.

By mentoring parents on the behavioral interventions that will encourage growth and development while in the NICU, parents are given a head start when they bring the baby home. Discharge planning that considers all the behavioral implications of procedures, feeding, sleep–wake cycles, and the physical environment at home is critical to ongoing care.

8.4. Vulnerability. A prolonged hospitalization in an NICU, combined with wires, tubes, and monitors necessary for survival, creates a sense of fragility and vulnerability. The "vulnerable child syndrome" that is a result of a neonatal intervention may occur with benign, self-limited conditions such as hyperbilirubinemia with phototherapy in some families, as well as after a serious medical condition (549, 550).

Infants with severe CLDI, in fact, are quite fragile. Their life hinges on assisted ventilation, a prolonged course of oxygen therapy, and adequate caloric intake to allow pulmonary maturation and somatic growth. Added to this burden is the prolonged NICU hospitalization, which often creates for the parents a sense of dependency on medical personnel and technology. Even for those infants for whom the home oxygen requirement and cardiopulmonary monitoring are relatively brief and adequate somatic growth is established, some parents may continue to perceive their child as vulnerable to illness and psychological problems for many years. The long-term outcome of these children, who continue to be perceived by their parents as excessively vulnerable, can be marked by excessive parental concerns about the health and development of the child, medical visits for minor symptoms, underestimation of the child's developmental potential, separation problems, sleep problems, and resistance to limit setting.

To prevent an exaggerated sense of vulnerability, a variety of interventions in the NICU can be planned as part of the care for all infants with CLDI (Table 5). These prevention measures should be continued after discharge, during office visits, and by home care health workers.

9. Ophthalmology. On the basis of the resiliency of the retinal vasculature once growth to the ora is complete, the retina of the fully vascularized former premature infant may be considered "safe" from mildly elevated arterial oxygen levels. This is assumed also to be true for the retinas of premature infants who have undergone peripheral retinal ablation (cryotherapy or laser therapy) of severe ROP, as these infants have no residual avascu-

TABLE 5. PREVENTION OF VULNERABLE CHILD SYNDROME–CHRONIC LUNG DISEASE OF INFANCY

Prevention (in NICU)
Keep parents informed about medical issues
Encourage parents to express concerns
Support parents' appropriate perspective, attitudes, and plans
Work with parents when distorted perceptions or unsuitable plans are apparent
Do not use terms that suggest a diagnostic entity when there is no real evidence supporting it, e.g., "allergy," "colitis"
Mobilize family support when needed
Management (in office)
A detailed physical examination (while narrating findings) to emphasize child's physical, developmental, and behavioral strengths
Discuss events in NICU and parental responses to them
Assist parents to establish relationship between reactions in NICU and present problem or perception of a problem
Encourage parents to perceive and handle child in an appropriate manner—physically and developmentally
Teach and role model appropriate limit setting
Refer for psychiatric evaluation and treatment if necessary

Definition of abbreviation: NICU = neonatal intensive care unit.
Modified from Levine and coworkers (574).

lar retina, nor any remaining immature retinal growing capillaries. The problems arise in those oxygen-dependent infants with peripheral avascular retina, with or without active ROP. These infants clearly remain at risk for ROP progression, and the best information we have, albeit weak, requires physicians to administer oxygen to these infants with care, with monitoring to avoid sustained hyperoxemia.

Until more recently, Pa_{O_2} levels of 95–100 mm Hg were considered unsafe for the retinal vessels of the premature infant's eyes, and values of 50–80 mm Hg were targeted instead, approximating oxygen saturations of 90–95%. This recommendation was accepted practice in the early days after birth, despite little evidence to document its safety and efficacy. It was considered a rational compromise between fetal arterial Pa_{O_2} (about 25–45 mm Hg) and the level a healthy preterm infant would have while breathing room air (90–95 mm Hg). New evidence about the safety of higher saturations targets has appeared (551). In the United States, a multicenter trial among oxygen-dependent premature infants with moderately severe ROP (STOP-ROP study) determined the effect on ROP of two different oxygen saturation targets, either 89–94 or 96–99% (463). In contrast to earlier opinion, this study found no adverse effects in infants with prethreshold ROP on progression to threshold ROP with the higher oxygen saturation targets. Thus, although unrestricted supplemental oxygen is to be avoided, saturation targets of 95–99% do not appear to increase, and in some cases may even decrease, risk of progression of ROP. This is reflected in the flow diagram of Figure 4. A multicenter trial being conducted in Australia (the BOOST study) (482) is studying the effects on growth, health, and development among infants with CLDI (irrespective of their ROP status) randomized to the same two target saturation ranges as used in the STOP-ROP trial.

Two issues arise in the home care of infants with unresolved ROP and CLDI, one with oxygen control, and the other with completion of follow-up care. Parents cannot usually be expected to provide close oxygen control and pulse oximetry at home without extensive support. To the extent that poor control of oxygenation may lead to worsening of the ROP, or occurrence of ROP in the incompletely vascularized eye, this poses a potential threat.

At least as important, however, is the stress placed on these families and how this can lead to missed follow-up appointments to the ophthalmologist. When an infant still at risk for ROP progression to threshold goes home, the chances decrease that detection and treatment of the threshold ROP (if it develops) will be timely and effective. Peripheral ablation for threshold ROP has proved effective (552, 553) in reducing blindness from ROP, and it is a tragedy for an infant to successfully transition to home, only to go blind without the opportunity for treatment because of missed follow-up appointments. In general, ROP that is regressing with vessels that have passed into Zone 3 on at least two sequential examinations is extremely unlikely to progress to threshold ROP or any vision loss (554). Infants whose vessels and/or ROP are still in Zone 1 or Zone 2 are at a higher risk for progression to threshold (555) and are a special challenge for the discharge planner and family. In such infants, ophthalmology visits should be scheduled every 1–2 weeks to monitor for progression, depending on the severity of the ROP. The incidence and severity of ROP are decreasing in some centers, possibly because of scrupulous monitoring of oxygen levels early in life as well as early aggressive ophthalmologic intervention (481). It may be decreasing for other unrecognized reasons as well, such as decreased incidence of intraventricular hemorrhage.

10. Well-child care. In addition to their specialized needs, infants with CLDI have all the usual requirements for well-child care. Indeed, the vulnerability of infants with CLD toward complications of lower respiratory infections during the first year or two of life makes prevention paramount. Counseling about smoking and allergens/irritants in the home assumes special significance. Avoidance of multichild day care settings is recommended along with the proven protective effects of hand washing.

The introduction of respiratory syncytial virus passive immunization with polyclonal and monoclonal antibody preparations provides a significant degree of protection against severe disease requiring hospitalization, but not against infection (556, 557). In addition, influenza immunization of the child (when old enough) and the care takers is also recommended.

It is important to counsel parents that infants with CLD affected by a lower respiratory infection frequently require an escalation in care. The child in whom supplemental oxygen has been discontinued may require its reinstitution for a length of time. The child receiving oxygen may require ventilator support. Such a pattern is common and usually reversible, but causes considerable anxiety for all involved.

11. Ethical issues. Ethical concerns tend to arise at certain nodal points in the care of children with chronic lung disease. Ethical decisions regarding the lower limits of viability in very preterm infants have been discussed extensively elsewhere (558).

Another major ethical decision point occurs for children who are unable to be weaned from mechanical ventilation, or who require institution of mechanical ventilation without any likelihood of weaning any time soon. The decision-making process involved has been discussed in several thoughtful articles (559, 560). Guidelines for helping with decisions regarding long-term

mechanical ventilation were proposed by Farrell and Fost (560). They suggested (*1*) obtaining the correct facts on prognosis (good ethics start with good facts); (*2*) avoiding irreversible decisions under uncertainty; this in general argues in favor of instituting ventilation in patients with severe CLDI, because it often improves over time, but of course concomitant medical conditions must be considered as well; (*3*) remembering that withdrawing treatment is ethically preferable to withholding it; (*4*) resolving disagreements with the use of outside consultation, for example, ethics committees; (*5*) including the entire family in the decision-making process; (*6*) remembering that consent is a process, not an event; and (*7*) identifying one primary health care provider who assumes responsibility for the key discussions regarding major medical decisions.

Discharge planning from the neonatal intensive care unit brings its own set of ethical concerns, as discussed in Section IV.A (Transitioning the Child with CLDI from Hospital to Home). Difficult decisions must be made in addressing the degree of technology necessary to enable a child with chronic respiratory failure, and growth and developmental problems, to be discharged from hospital. The relative roles of family and society in the care of these children vary from one country to another, and in many cases depends on differences in health care system structure and insurance coverage.

In very ill children with CLDI, two other areas that require ethical considerations are lung transplantation and terminal care.

11.1. Lung transplantation. In rare instances, all of the above-described means of supporting the infant with CLDI fail. In such instances, consideration can be given to lung transplantation. Lung transplantation has been attempted in a handful of infants with CLDI (561, 562); living related lobar donor procedures have been performed. There is not enough long-term experience with this procedure to be able to predict ultimate outcome and whether the transplanted lung will have the growth potential necessary to sustain the patient for his or her lifetime.

11.2. Terminal care. On occasion a child with CLD will be at the stage where terminal care is warranted. The same experience and approaches for home death and bereavement that have been successfully applied to children with terminal oncologic problems or late-stage cystic fibrosis can be utilized (563–566). Fortunately, with improvements in care this is rarely warranted.

V. CONCLUSIONS AND CLINICAL RESEARCH QUESTIONS

In summary, CLDI is a multisystem disorder that affects more than just the lungs, and is likely to remain a lifelong condition, albeit decreasing in severity with growth. Whether severity decreases or increases with further aging is unknown. Although there are several good randomized clinical trials that have investigated the effects of various treatments on the development of CLDI, there is little information from controlled clinical trials on treatment of established CLDI throughout childhood and adulthood.

The following is a compilation of some of the important areas that should be addressed in the next decade of research into the care of children with CLDI. There are many questions worthy of exploration; the following list is neither exhaustive nor exclusive. Most importantly, many of these questions would require large, well-designed, multicenter prospective studies to answer. Mechanisms for funding such studies should include support for coordinating centers, modeled after such studies as the Primary Pulmonary Hypertension Registry supported by the NIH or the Therapeutic Development Center Network supported by the Cystic Fibrosis Foundation.

A. Epidemiology

1. What is the best definition of BPD? How does supplemental oxygen requirement at 36 weeks postconceptional age differ from than an oxygen requirement at 28 days of life as a predictor of subsequent CLDI?
2. Is the incidence of BPD increasing or decreasing? Surfactant therapy would be expected to have competing effects: higher survival rates of lower birth weight infants in whom RDS and BPD are more prevalent versus possible reduction in incidence of RDS/BPD in a given cohort of birth weights. Are we saving more premature, higher risk infants? Are there clinically important differences between the "new" BPD and "old" BPD as these infants grow into children with CLD?
3. As newer therapies are introduced (e.g., antioxidant and antiinflammatory agents), will they affect the prevalence of CLDI? Will newer ventilatory strategies aimed at decreasing barotrauma (e.g., high-frequency oscillatory ventilation and liquid ventilation) decrease the incidence of CLDI?
4. What is the natural history of lung function changes in CLDI? Do children with CLDI become adults with COPD?

B. Pulmonary and Airway Injury

1. Pathophysiology.

a. What is the relative importance of barotrauma and oxygen toxicity in causing CLDP and CLDI? Further work is needed to elucidate the roles of inflammatory mediators in CLDP and CLDI pathogenesis.
b. Do high-frequency ventilation, liquid ventilation, nitric oxide therapy, extracorporeal membrane oxygenation, and antioxidant and antiinflammatory therapies interrupt the pathogenetic process?
c. Is early diuresis important in the ultimate development of CLDP and CLDI?
d. What are the mechanisms of central airway injury? Are they similar to those for pulmonary parenchymal injury? What additional role does the presence of an artificial airway play? How do various modes of ventilatory strategy (intermittent mandatory ventilation, synchronized intermittent mandatory ventilation, assist control, liquid ventilation) or alternative patient–ventilator interfaces (nose mask, nasal prongs, negative pressure body ventilators) affect the development of central airway injury?
e. What is the role of intrinsic factors such as initial lung size, airway size, and atopy in determining the outcome of CLDI? Do the genotype/phenotype correlations currently being investigated for asthma have a role in determining "susceptibility" to developing CLDI and its long-term consequences? Are there other genetic risk factors for CLDI, for example, polymorphisms in surfactant protein genes?
f. What is the role of airway remodeling in the development of CLDI? Does the airway hyperreactivity in infancy and childhood predispose to fixed airway obstruction in adulthood apart from the structural airway abnormalities present at birth?
g. How does smoking (passive or active) interact with CLDI to affect adult lung function?

2. Diagnostics.

a. What is the relationship between bronchoalveolar lavage fluid inflammatory markers of lung injury and alterations in lung function?
b. What are the advantages of following lung function tests in infants with CLDI? Are the benefits worth the costs?

c. What role does respiratory muscle fatigue play in the development of chronic respiratory failure in infants and children with CLDI? What are the best tests for assessing respiratory muscle fatigue?
d. What is the natural history of the alterations in lung function, central airway function, airway hyperreactivity, exercise function, and lung function decline in adult life?

3. Therapeutics.

a. How can animal models that explore BPD pathogenesis be used to explore preventative and treatment strategies for BPD and CLDI?
b. What is optimal pharmacotherapy of CLDI? What are the effects of antiinflammatory and bronchodilator agents on pulmonary function and improvement in lung function with time? For example, a number of substantial questions remain about the use of systemic and nebulized corticosteroids: Who should be treated? When should treatment be started? What is the best therapeutic regimen? How long should treatment be continued? What is the risk-to-benefit ratio? Is it possible to identify infants at high risk of developing BPD and initiate steroid therapy earlier in those infants? What is the role of cromolyn sodium? What is the role, if any, of leukotriene receptor antagonists? Can chronic antiinflammatory therapy prevent airway remodeling in patients with CLDI as they age? All studies investigating pharmacotherapy of CLDI should be controlled, blinded, and prospective to provide information suitable for the practice of evidence-based medicine.
c. What are the best pharmacologic treatments and ventilatory strategies for treating abnormally high central airway compliance?
d. What are the risk-to-benefit ratios of maintaining oxygen saturation *vis à vis* risk of cor pulmonale versus risk of ROP?
e. What is the minimal oxygen saturation necessary for adequate growth?
f. What are the indications for, referral criteria for, and long-term pulmonary outcome of lung transplant for CLDI?

C. Respiratory Control during Sleep: Relationship between Chronic Lung Disease of Infancy and Sudden Infant Death Syndrome

1. Does cardiorespiratory monitoring enhance the safety of infants with CLDI? Which infants?
2. What are the indications for performing tests of control of breathing in infants with CLDI? Which tests should be performed?
3. Does supplemental oxygen decrease the incidence of sudden infant death syndrome (SIDS) in infants with CLDI?

D. Cardiac Complications

1. What is the best way to monitor for the development of pulmonary hypertension and cor pulmonale? What is the sensitivity and specificity of the ECG in this patient group for the diagnosis of cor pulmonale? Of the echocardiogram? In what percentage of patients can pulmonary pressure be estimated by Doppler echocardiography?
2. It is necessary to further define the role of inhalational nitric oxide for patients during acute pulmonary exacerbations. What is the ideal dose of NO? What is the frequency of complications? What impact does such adjuvant therapy have on outcome and length of admission?
3. What is the role of cardiac contractility studies in this patient population? What are the relative roles of quantitating left ventricular and right ventricular contractility with dP/dT echocardiographic studies and radionuclide scans?
4. Is there a role for CPAP in increasing left ventricular function by increasing pleural pressure, thereby decreasing left ventricular afterload?
5. Is there a role for magnetic resonance angiography in defining cardiovascular complications of BPD?

E. Nutrition and Gastrointestinal Complications

1. What are the relationships between somatic growth and lung growth?
2. What is the role and what are the indications for mechanical ventilation in promoting somatic growth by decreasing the caloric expenditure of the work of breathing?
3. What are the relative roles of the work of breathing versus metabolic cost of pulmonary inflammation in the excessive caloric expenditure of infants with CLDI?
4. What are the best ways to assess nutritional status? What is the clinical utility of skinfold thickness measurement and bone densitometry?
5. What is the role of aspiration lung diseases in perpetuating the lung damage of CLDI, and what is the role of treatment of aspiration in resolving CLDI?
6. Do techniques of feeding and stimulating development of oral–motor function allow infants with CLDI to progress more rapidly to full oral feeding?
7. Development of postnatal premature growth curves against which to plot the growth of infants with comparable degrees of prematurity and CLDI.

F. Renal Complications

1. What are the best ways to prevent and treat renal stones and disordered calcium metabolism due to diuretic use?
2. What is the pathophysiology of systemic hypertension in infants with CLDI, and what are the best ways to treat it?
3. What is the natural history of renal function into adolescence and adulthood? Is there an increased prevalence of chronic renal disease/renal failure in adults with a history of CLDI? Is there an accelerated loss of renal function with aging?

G. Neurodevelopmental Complications

1. What are the relative roles of CLDI versus prematurity per se in neurodevelopmental outcome?
2. What are the effects on neurodevelopmental outcome of newer developments in therapy of CLDP, for example, ventilator management strategies, surfactant therapy, and antiinflammatory and antioxidant therapy?
3. What is the natural history of childhood developmental disabilities associated with CLDI, for example, attention deficit–hyperactivity disorder/pervasive developmental disorder, vulnerable child syndrome?

H. Ophthalmologic Complications

1. At what postconceptional age and stage of retinal development is it safe to liberalize supplemental oxygen to maintain a saturation of greater than 95%?
2. What is the natural history of ROP into adolescence and adulthood? What are the best therapies to halt progression to blindness?

I. Home Care of the Child with Chronic Lung Disease of Infancy

1. What are the effects of specific interventions (e.g., home cardiorespiratory or oximetry monitoring, home nursing,

case management), on long-term outcomes for infants and families?
2. What is the effectiveness of specific teaching strategies in preparing families for discharge from acute care settings?
3. What are the optimal techniques for tracheostomy care (e.g., suctioning, cleaning of tubes, frequency of tube changes)?
4. What are ethical aspects of home care (e.g., defining relative risks and benefits, scope of parental and professional responsibility)?

J. Well-Child Care of the Child with CLDI

Better definition is needed of the risk factors for severe lower respiratory illness in infants with CLDI and also infected with respiratory syncytial virus.

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