



## New Coding in the *International Classification of Diseases, Ninth Revision*, for Children's Interstitial Lung Disease

Jonathan Popler, MD, FCCP; Burton Lesnick, MD, FCCP; Megan K. Dishop, MD; and Robin R. Deterding, MD

The term “children's interstitial lung disease” (chILD) refers to a heterogeneous group of rare and diffuse lung diseases associated with significant morbidity and mortality. These disorders include neuroendocrine cell hyperplasia of infancy, pulmonary interstitial glycogenosis, surfactant dysfunction mutations, and alveolar capillary dysplasia with misalignment of pulmonary veins. Diagnosis can be challenging, which may lead to a delay in recognition and treatment of these disorders. Recently, *International Classifications of Diseases, Ninth Revision* codes have been added for several of the chILD disorders. The purpose of this article is to give an overview of the chILD disorders and appropriate diagnostic coding. *CHEST* 2012; 142(3):774–780

**Abbreviations:** ABCA3 = ATP-binding cassette family of transports member A3; ACDMPV = alveolar capillary dysplasia associated with misalignment of pulmonary veins; chILD = children's interstitial lung disease; DIP = desquamate interstitial pneumonia; ICD-9 = *International Classification of Diseases, Ninth Revision*; NEHI = neuroendocrine cell hyperplasia of infancy; NSIP = idiopathic nonspecific interstitial pneumonitis; PIG = pulmonary interstitial glycogenosis; SP-B = surfactant protein B; SP-C = surfactant protein C; TTF-1 = thyroid transcription factor 1

The term “children's interstitial lung disease” (chILD) refers to a heterogeneous group of rare and diffuse lung diseases associated with significant morbidity and mortality.<sup>1</sup> These diseases include neuroendocrine cell hyperplasia of infancy (NEHI), pulmonary interstitial glycogenosis (PIG), surfactant dysfunction mutations, and alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV), which are more common in infancy. As many of these disorders may involve areas of the lung other than the interstitium, some literature refers to these disorders as

pediatric diffuse lung diseases. There can be a high morbidity and mortality associated with chILD disorders, especially when they exist with pulmonary hypertension.<sup>2</sup> Diagnosis can be challenging, which may lead to a delay in recognition and treatment of these disorders. In an effort to improve recognition of these disorders, several reviews of pathologic specimens have been completed to more fully define the classification of chILD disorders.<sup>2,3</sup>

In the *International Classification of Diseases, Ninth Revision* (ICD-9), codes have been added for several of the chILD disorders as subheadings under the general heading of “Other alveolar and parietoalveolar pneumonopathy” (ICD-9 code heading 516). ICD-9 is the official system in the United States for assigning codes to diagnoses associated with hospitalization and is governed by National Center for Health Statistics and the Centers for Medicare and Medicaid Services.<sup>4</sup> Additionally, ICD-9 codes are often used to facilitate disease tracking, monitor procedures performed, and play a role in physician reimbursement. These codes will likely be adopted by the World Health Organization in future revisions. Regardless, ICD-9 codes are an important step

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**Affiliations:** From the Georgia Pediatric Pulmonology Associates (Drs Popler and Lesnick), Atlanta, GA; the Department of Pathology (Dr Dishop), University of Colorado Denver School of Medicine, Children's Hospital Colorado; and the Department of Pediatrics (Dr Deterding) University of Colorado Denver, Aurora, CO.

**Correspondence to:** Jonathan Popler, MD, FCCP, Georgia Pediatric Pulmonology Associates, 1100 Lake Hearn Dr, Ste 450, Atlanta, GA 30342; e-mail: JPopler@gppa.net

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forward in the United States to statistically track these new diseases, providing opportunities for better identification and disease monitoring. The purpose of this article is to give an overview of the chILD disorders and provide guidance on new appropriate ICD-9 coding (Table 1).

NEUROENDOCRINE CELL HYPERPLASIA  
OF INFANCY (ICD-9 CODE 516.61)

NEHI, previously referred to as persistent tachypnea of infancy, was first described in 2001.<sup>5</sup> It is a respiratory disorder of unknown cause, typically presenting in the first year of life with tachypnea, retractions, crackles, and hypoxemia.<sup>5,6</sup> Often, a characteristic pattern can be noted on high-resolution CT scan, consisting of ground-glass opacities most commonly occurring in the right middle lobe and lingula (Fig 1). Air trapping may be noted in the lower lobes.<sup>7-9</sup> In patients with NEHI who underwent infant pulmonary function testing, air trapping and airway obstruction were noted when compared with disease control subjects.<sup>10</sup> The diagnostic gold standard of NEHI remains a lung biopsy showing increased numbers of bombesin-immunopositive pulmonary neuroendocrine cells within bronchioles and alveolar ducts without evidence of other abnormalities, and limited or absent inflammation (Fig 2).<sup>11,12</sup> Although the diagnostic gold standard is lung biopsy, an experienced center in chILD may be able to establish a diagnosis of NEHI using clinical presentation, classic high-resolution CT scan findings, and consistent infant pulmonary function data.<sup>13</sup> The evaluation of BAL of patients with NEHI also fails to show high numbers of inflammatory cells or cytokines.<sup>14</sup> Several novel diagnostic methods have been investigated, including the assessment of KL-6 levels and novel biomarkers.<sup>15,16</sup> The treatment of NEHI remains supportive, and includes oxygen supplementation. Nutrition must be optimized, as failure to thrive may be seen in infants with this disorder.<sup>6,13</sup> Common practice has been to treat with steroid bursts during upper respiratory tract infections and wheezing episodes.

**Table 1—New ICD-9 Codes More Common in Infancy and Childhood**

ICD-9 Code	Disorder
516.6	Interstitial lung diseases of childhood
516.61	Neuroendocrine cell hyperplasia of infancy (NEHI)
516.62	Pulmonary interstitial glycogenosis (PIG)
516.63	Surfactant mutations of the lung
516.64	Alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV)
516.69	Other interstitial lung diseases of childhood

ICD-9 = *International Classification of Diseases, Ninth Revision*.



**FIGURE 1.** High-resolution CT scan with ground-glass opacities in the right middle lobe, lingula, and central lung fields in a patient with neuroendocrine cell hyperplasia of infancy.

However, the long-term use of chronic corticosteroids is not recommended.<sup>13</sup>

Outcomes in NEHI are excellent, with no mortality reported. However, the disease burden can be quite high, with months to years of supplemental oxygen required. As mentioned previously, some children may require supplemental feeds and the placement of gastrostomy tubes. Additionally, some patients with NEHI continue to have air trapping and symptoms such as dyspnea with exercise into their teenage and early adult years.<sup>17</sup> Cases of NEHI have been reported in families, suggesting a potential genetic basis for disease.<sup>18</sup> The appropriate coding for NEHI will enhance our understanding of the potential genetic link and natural history into adulthood.

SURFACTANT DYSFUNCTION  
MUTATIONS (ICD-9 CODE 516.63)

In infants born prior to full gestational age, the inadequate production of surfactant, a mixture of lipids and proteins required to reduce alveolar surface tension, is the primary cause of respiratory distress syndrome.<sup>19,20</sup> There are three different proteins with important roles in surfactant function and metabolism: surfactant protein B (SP-B), surfactant protein C (SP-C), and an ATP-binding cassette family of transports member A3 (ABCA3). Mutations in any of the genes encoding for the three different proteins can result in significant lung disease.<sup>21</sup> Patients with surfactant metabolic dysfunction disorders can present with respiratory failure immediately at birth or later in childhood, often depending on the specific mutation.

The first recognized genetic cause of surfactant dysfunction was due to an inability to produce SP-B.<sup>22</sup> The majority of cases are caused by the common

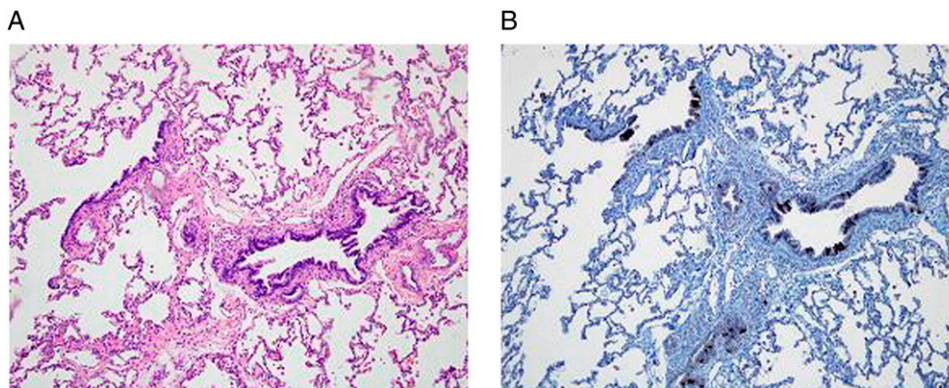


FIGURE 2. Histologic features of neuroendocrine cell hyperplasia of infancy include the absence of significant inflammation or fibrosis of the bronchioles on routine hematoxylin and eosin (H&E) staining and the presence of increased bombesin-positive airway neuroendocrine cells in the respiratory bronchioles and alveolar ducts. A, H&E, original magnification  $\times 25$ . B, bombesin immunohistochemistry, original magnification  $\times 25$ .

SP-B mutation 121ins2, which when homozygous is lethal without lung transplantation.<sup>21</sup> Infants with an inability to produce SP-B typically have significant respiratory distress and radiographic evidence of diffuse lung disease several hours after birth.<sup>23-26</sup> Lung disease is rapidly progressive over the next several months, with affected patients requiring maximal medical therapy, including mechanical ventilation and extracorporeal membrane oxygenation.<sup>21</sup> Most affected patients will require lung transplantation in infancy, although some infants with milder mutations, who may still have some surfactant production, may not require transplantation.<sup>27-30</sup>

SP-C mutations were described as causing pulmonary disease in 2001.<sup>31</sup> Patients heterozygous for one SP-C mutation can have a variable clinical course and presentation, with patients identified from the neonatal period to adulthood. The most common SP-C mutation is p.Ile73Thr, occurring in about 30% of people with SP-C mutations. Approximately one-half of the SP-C mutations arise de novo in the affected individual.<sup>21</sup> Clinical severity can also vary, including hypoxemia, failure to thrive, and persistent infiltrates on chest radiograph.<sup>32-35</sup> Treatment remains variable and often depends on severity of the affected patient. In more severely affected patients, lung transplantation may be offered. However, it should be noted that in infants, clinical improvement can often occur even after years of mechanical ventilation. Case reports suggest corticosteroids and hydroxychloroquine may be of some use.<sup>36,37</sup>

ABCA3 deficiency is a more recently described surfactant dysfunction mutation disorder with an autosomal recessive inheritance pattern. Patients with ABCA3 deficiency have a highly variable clinical course.<sup>38,39</sup> Many patients can present with significant lung disease in infancy; however, later presentations have been reported.<sup>38-44</sup> Prolonged survival is

also being recognized. The most common mutation reported is the E292V mutation, which has been associated with milder disease.<sup>45</sup> Treatment may include oxygen, nutritional supplementation, mechanical ventilation, and courses of oral or pulse glucocorticoid therapy.<sup>21</sup> Lung transplantation has also been successfully performed for patients with persistent respiratory failure as newborns or end-stage lung disease with ABCA3 mutations.

Thyroid transcription factor 1 (TTF-1), also known as Nkx2.1 or TITF1, is one of a number of transcription factors important for the expression of several genes involved in surfactant production and function, including surfactant protein A, SP-B, SP-C, and ABCA3.<sup>21</sup> Mutations in TTF-1 present with a variety of conditions, including choreoathetoid movements or hypotonia, hypothyroidism, and pulmonary disease.<sup>46-48</sup> The term brain-thyroid-lung syndrome has been used to describe the phenotype.<sup>49-52</sup> Brain-thyroid-lung syndrome, or TTF-1 mutations, should be suspected in any patient with hypothyroidism, neurologic symptoms, and respiratory disease. A high index of suspicion is necessary, as the complete triad, especially hypothyroidism, may not always exist in all patients with mutations. Both the lung histology and clinical disease can be quite variable, from severe life-threatening disease in the newborn period requiring a lung transplant to chronic lung disease and patterns of recurrent pulmonary infections. Mutations in only one gene produce disease by decreasing the amount of protein produced or a haploinsufficiency state. Additionally, gene deletions have been reported as a cause of the haploinsufficiency state. No common mutation has currently been recognized.<sup>53</sup>

Recently, mutations in the  $\alpha$ -chains (*CSF2RA*) and affinity-enhancing  $\beta$ -chains of the (*CSF2RB*) granulocyte-macrophage colony-stimulating factor receptor have also been identified in children.<sup>54</sup> Although



not mutations involved in surfactant protein production, granulocyte-macrophage colony-stimulating factor receptor mutations result in abnormal catabolism. The radiographic and pathologic result is pulmonary alveolar proteinosis. Although further refinement in coding may define these different types of surfactant dysfunctions, currently all mutations involving surfactant dysfunction should be coded in this category.<sup>21</sup>

Appropriate coding for surfactant dysfunction mutations is critical to track disease in families, to establish the incidence and prevalence of these genetic diseases, and to capture the variable phenotypes and natural history. All potentially disease-causing mutations should be coded as surfactant mutations of the lung, even if only a single copy is present.

#### PULMONARY INTERSTITIAL GLYCOGENOSIS (ICD-9 CODE 516.62)

PIG was first reported in a seven-patient case series in 2002.<sup>55</sup> The hallmark pathologic findings in PIG on electron microscopy are round, glycogen-laden mesenchymal cells that increase the width of the pulmonary interstitium.<sup>56</sup> Many experienced pediatric lung pathologists can now recognize this disorder on hematoxylin and eosin staining without the use of electron microscopy or other special stains. The true function of these cells is unclear, but histology staining has shown that these cells are mesenchymal in origin and can proliferate, potentially expanding the interstitial space.<sup>56</sup> As PIG has not been seen past 8 months of age, a developmental association is postulated.<sup>13</sup>

Patients with PIG may present in the neonatal period with retractions, tachypnea, and oxygen requirement out of proportion to the clinical situation.<sup>13</sup> PIG has also been reported in association with children with hemodynamically significant cardiac disease.<sup>56</sup> There is one case report describing PIG in monozygotic 31-week preterm twins.<sup>57</sup> A lung biopsy is currently required for diagnosis. On lung biopsy, two characteristic patterns of PIG have been observed: diffuse interstitial PIG without growth abnormalities, or so-called patchy PIG involvement in preterm patients with alveolar growth abnormalities (Figs 3A, 3B).<sup>13</sup> Both conditions should be coded as PIG.

Treatment includes oxygen supplementation as required, optimizing nutritional status, and a short course of glucocorticoid therapy after weighing the risks and benefits of glucocorticoids, based on anecdotal reports of impressive clinical response.<sup>56</sup> In keeping with the varied nature of presentation and heterogeneity of the disorder, clinical outcomes can be quite varied. No mortality has been reported in cases of PIG existing in isolation. However, deaths have been reported when PIG exists in concert with

cardiovascular disease, such as pulmonary hypertension, or other alveolar growth abnormalities.<sup>13</sup>

#### ALVEOLAR CAPILLARY DYSPLASIA ASSOCIATED WITH MISALIGNMENT OF PULMONARY VEINS (ICD-9 CODE 516.64)

ACDMPV is a rare disorder of early lung development. More than 200 cases have been reported, including 10% with a familial history suggestive of an autosomal recessive inheritance pattern.<sup>58</sup> The most common presentation is in term infants during the neonatal period with respiratory failure and pulmonary hypertension. Despite aggressive interventions, including therapy for pulmonary hypertension, immediate endotracheal intubation with ventilation, and extracorporeal membrane oxygenation, the disorder is almost universally fatal.<sup>59</sup> The underlying mechanisms of disease are usually unknown. Reports of microdeletions in the *FOX* gene cluster on 16q24.1 and mutations of *FOXF1* have been associated with cases of ACDMPV and associated congenital anomalies, such as hypoplastic left heart, intestinal malrotations or atresias, or renal abnormalities.<sup>58,59</sup> Diagnosis is currently made by lung biopsy or postmortem examination, as clinical testing for *FOXF1* is not currently widely available.

Treatment of this rare and fatal disease is limited. Currently, lung transplantation remains the only treatment option, although the rapid progression of respiratory failure in ACDMPV may make transfer to an appropriate center difficult.<sup>13</sup>

#### OTHER INTERSTITIAL LUNG DISEASES OF CHILDHOOD (ICD-9 CODE 516.69)

Other interstitial lung diseases, not otherwise specified, should be classified using this code. As further differentiation of these disorders progresses, there may be an opportunity for more refined coding in the future. Other diagnoses seen in children with *chILD* but more common in adolescence or adulthood (see "Coding Considerations") should also be coded as Other Interstitial Lung Disease of Childhood (ICD-9 code 516.69) in addition to the primary code, to distinguish that this disease has occurred in children.

#### NEW ICD 9 CODES SEEN IN *chILD* AND ADULTS

New ICD-9 codes were also released for diseases that are more commonly seen in adults but can also be seen in *chILD* (Table 2). These codes closely follow the classification of the idiopathic interstitial pneumonias in adults that included seven clinico-radiologic-pathologic entities: idiopathic pulmonary

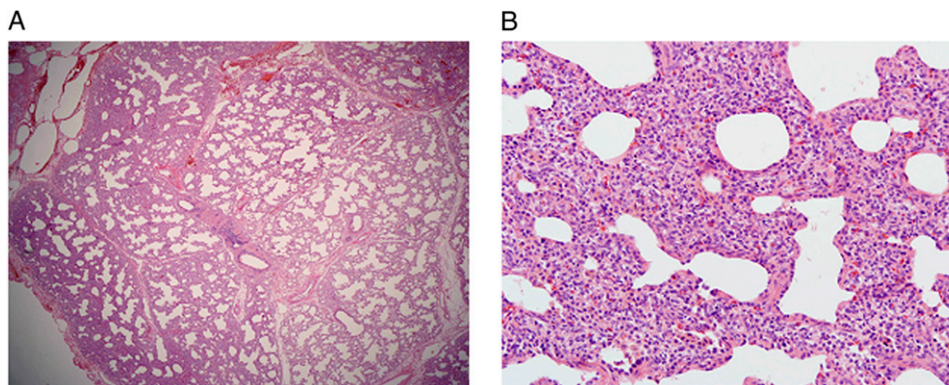


FIGURE 3. Pulmonary interstitial glycogenosis (PIG) is characterized by interstitial widening due to increased numbers of mesenchymal cells. A, This example demonstrates abnormal alveolar growth (alveolar simplification), characterized by enlarged and poorly septated airspaces at low power, as well as variable interstitial widening (H&E, original magnification  $\times 25$ ). B, At higher power, the interstitial cellularity is composed of bland ovoid nuclei with surrounding clear cytoplasm, typical of PIG (H&E, original magnification  $\times 25$ ). See Figure 2 legend for expansion of the abbreviation.

fibrosis, nonspecific interstitial pneumonia, cryptogenic organizing pneumonia, acute interstitial pneumonia, respiratory bronchiolitis-associated interstitial lung disease, desquamative interstitial pneumonia (DIP), and lymphoid interstitial pneumonia.<sup>60</sup> Of these entities, idiopathic pulmonary fibrosis and respiratory bronchiolitis-associated interstitial lung disease are not believed to occur in children. Although a complete review of each entity is outside the scope of this article, the reader should be aware of specific issues that impact children in some of these disorders.

Idiopathic nonspecific interstitial pneumonitis (NSIP) (ICD-9 code 516.32) is a code used when the cause of the disease is unknown. NSIP is less common in younger children and is usually seen in older children and adolescents. Typical lung pathology shows a diffuse interstitial infiltration of lymphocytes (Fig 4). NSIP can be idiopathic or exist in association with surfactant mutations or collagen vascular disease.

**Table 2—New ICD-9 Codes Seen in Children and Adults**

ICD-9 Code	Disorder
516.32	Idiopathic nonspecific interstitial pneumonitis (NSIP)—excludes due to known underlying disease
516.33	Acute interstitial pneumonitis
516.35	Idiopathic lymphoid pneumonia—excludes due to known underlying disease
516.36	Cryptogenic organizing pneumonia—excludes due to known underlying disease
516.37	Desquamative interstitial pneumonia—excludes due to known underlying disease
516.8	Other specified alveolar and parietoalveolar pneumonopathies (due to known underlying disease)
	Lymphoid interstitial pneumonia (LIP)
	Nonspecific interstitial pneumonia (NSIP)
	Organizing pneumonia

See Table 1 legend for expansion of abbreviation.

For example, both SP-C and ABCA3 mutations have been associated with pathologic diagnoses of NSIP.<sup>34,41</sup> When a specific diagnosis is known, it should be coded first followed by NSIP due to known underlying cause (516.8). NSIP can cause significant morbidity and mortality in older children.

Specific information related to children for the other idiopathic interstitial pneumonias is briefly reviewed. Acute interstitial pneumonia (516.33) is rare in children but is a rapid idiopathic progression of diffuse interstitial disease that histologically resembles diffuse alveolar damage. Idiopathic lymphoid pneumonia (516.35) in children is most commonly associated with immunocompromised status seen with HIV and immunodeficiency and lymphoproliferative disease in children. Cryptogenic organizing pneumonia (516.36) was

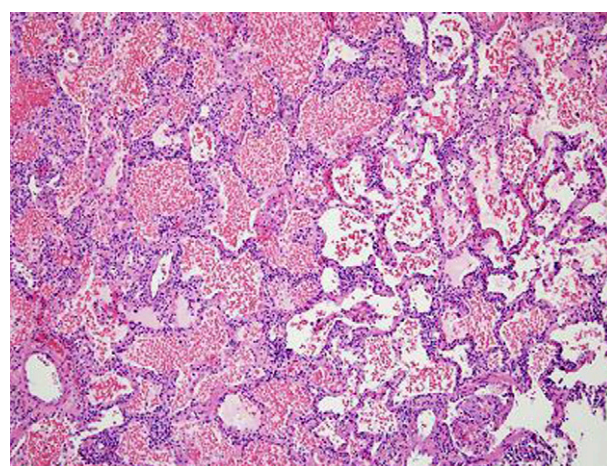


FIGURE 4. Another form of interstitial lung disease in children is nonspecific interstitial pneumonia. Lung pathology is characterized by a diffuse mild to moderate interstitial infiltrate of lymphocytes. This case also shows increased alveolar macrophages and hemorrhage within the airspaces (H&E, original magnification  $\times 25$ ). See Figure 2 legend for expansion of the abbreviation.



previously known as bronchiolitis obliterans with organizing pneumonia. Cryptogenic organizing pneumonia can be seen in children with infection, autoimmune disease, and posttransplantation (lung and bone marrow), drug reaction, and chemotherapy treatments. DIP (516.37) has been associated with surfactant dysfunction mutations. If DIP is noted on a pediatric lung biopsy specimen, testing for surfactant genetic abnormalities should be completed. If testing is negative, the diagnosis may be idiopathic DIP. Most idiopathic interstitial pneumonias in children are believed to respond to glucocorticoids.

## CODING CONSIDERATIONS

It is important to remember that to use the new codes for any child with interstitial lung disease the provider must note the specific type of lung disease in their documentation. When the diagnosis for an individual child has not yet been defined, it should be coded 516.6, interstitial lung diseases of childhood. Once a diagnosis has been established, it is appropriate to code more specifically using the new codes (Table 1). When children have any of the idiopathic interstitial pneumonias (Table 2), they should have the primary disease code (516.32-37) as well as the code 516.69 for other interstitial lung diseases of childhood to denote that this disease has occurred in childhood. ICD-10 codes are currently in development. It is anticipated there will be direct relationships for these new codes from ICD-9.

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