

Rare Lung Diseases

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LEARNING OBJECTIVES

1. Evaluate pharmacologic agents for airway clearance in pediatric patients with primary ciliary dyskinesia.
2. Design treatment of infections common in pediatric patients with primary ciliary dyskinesia.
3. Analyze the appropriateness of treatment options for acute pulmonary hemorrhage in a pediatric patient.
4. Assess published data on pharmacologic agents, including corticosteroids and immunosuppressive agents, and whole lung lavage regarding the treatment of pediatric interstitial lung diseases.

ABBREVIATIONS IN THIS CHAPTER

ANCA	Antineutrophil cytoplasmic antibody
CF	Cystic fibrosis
chILD	Childhood interstitial lung disease
DAH	Diffuse alveolar hemorrhage
DLD	Diffuse lung diseases
GM-CSF	Granulocyte-macrophage colony-stimulating factor
PAP	Pulmonary alveolar proteinosis
PCD	Primary ciliary dyskinesia
PET	Pressure equalization tubes
rFVIIa	Recombinant factor VIIa
SP-B	Surfactant protein B
SP-C	Surfactant protein C
WLL	Whole lung lavage

[*Table of other common abbreviations.*](#)

PRIMARY CILIARY DYSKINESIA

Primary ciliary dyskinesia (PCD) is a recessive genetic disorder characterized by uncoordinated and/or ineffective ciliary beat. Although difficult to estimate given the challenges presented by diagnostic approaches, the incidence of PCD is estimated at 1 per 10,000–20,000 births (Knowles 2016). Because of the small number of patients with PCD, morbidity and mortality are difficult to estimate. A 2016 longitudinal study in adult PCD patients found an incidence of all-cause mortality of 5% and a respiratory mortality of 3.3% (Shah 2016). Hallmarks of PCD include persistent wet cough, chronic nasal congestion or sinusitis, and recurrent otitis media. Situs inversus and situs ambiguous are also common in patients with PCD at rates of 50% and 12%, respectively (Daniels 2016). Patients with a triad of symptoms, including situs inversus, chronic sinusitis, and bronchiectasis as a result of PCD, receive the diagnosis of Kartagener syndrome.

Clinical manifestations of PCD begin in the neonatal period, with more than 80% of full-term infants experiencing respiratory distress manifesting as tachypnea, increased work of breathing, and supplemental oxygen requirement. Patients often receive a diagnosis of transient tachypnea of the newborn; however, PCD has a few important distinguishing features, including later onset of respiratory distress (12–24 hours after birth), longer duration of oxygen requirement, and higher frequency of atelectasis or lobar collapse (Mullowney 2014).

Greater than 80% of PCD patients have chronic nasal congestion or sinusitis, and almost 100% will have a persistent, wet, productive cough. Recurrent otitis media with chronic middle ear effusions also affects about 80% of children with PCD, which may result in hearing loss, speech and language delays, and the need for hearing aids. In addition, both male and female patients are likely to have reduced fertility (Shapiro 2016).

Diagnosis of PCD is particularly challenging and includes both clinical phenotype and diagnostic testing. Recent PCD Foundation consensus guidelines outline major clinical criteria, which include the following:

1. Unexplained neonatal respiratory distress (at term birth) with lobar collapse and/or need for respiratory support with continuous positive airway pressure and/or oxygen for more than 24 hours;
2. Any organ laterality defect;
3. Daily, year-round, wet cough starting in first year of life or bronchiectasis on chest CT; and
4. Daily, year-round nasal congestion starting in first year of life or pansinusitis on sinus CT (Shapiro 2016).

In patients 1 month and older with two clinical criteria, situs inversus totalis and unexplained neonatal respiratory distress at term birth, PCD should be investigated.

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- General knowledge of the pathophysiology that leads to respiratory infections in chronic lung diseases
- Drug knowledge of the antimicrobial agents used to treat common respiratory organisms
- Various immunosuppressive agents used to treat diffuse lung diseases, including the primary adverse effects associated with each
- General knowledge of the coagulation cascade and the mechanism of action for available factor products and other agents that affect clotting

[*Table of common laboratory reference values.*](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- American Thoracic Society. [Diagnosis of Primary Ciliary Dyskinesia: An Official American Thoracic Society Clinical Practice Guideline](#). *Am J Respir Crit Care Med* 2018;197:e24-39.
- Primary Ciliary Dyskinesia Foundation Consensus Recommendations. [Diagnosis, Monitoring, and Treatment of Primary Ciliary Dyskinesia: PCD Foundation Consensus Recommendations Based on State of the Art Review](#). *Pediatr Pulmonol* 2016;51:115-32.
- American Thoracic Society Committee on Childhood Interstitial Lung Disease. [Classification, Evaluation, and Management of Childhood Interstitial Lung Disease in Infancy](#). *Am J Respir Crit Care Med*. 2013;188:376-94.

Recommended diagnostic testing differs based on patient age and geographic location. In patients younger than 5 years, ciliary biopsy for electron microscopy and/or genetic studies are recommended for patients in North America versus the recommendation in Europe of ciliary biopsy for high-speed video microscopy analysis. These younger patients cannot cooperate fully with the required maneuvers for nasal nitric oxide measurement; therefore, this testing modality is not reliable. For patients 5 years and older, nasal nitric oxide testing is recommended, with a nasal nitric oxide during plateau of less than 77 nL/minute on two occasions more than 2 months apart as diagnostic of PCD. Ciliary biopsy for electron microscopy or high-speed video microscopy, depending on patient's country of residence, and/or genetic studies can be used in these older patients as needed for confirmation (Lucas 2017b, Shapiro 2016).

Genetic testing is also recommended as part of PCD diagnosis. Currently, 33 genes are known to be associated with PCD, all of which have an autosomal recessive pattern of inheritance except for two rare X-linked genes. New genes linked to PCD continue to be discovered, and genetic testing results may contain mutations of unknown clinical significance, so genetic counselling is recommended for all patients.

Because PCD is relatively uncommon, many of the recommendations for treatment and follow-up care are based on experience in patients with cystic fibrosis (CF) or bronchiectasis. It is recommended that patients establish a relationship with a physician at either a PCD Foundation clinical center or an accredited CF center for two to four visits annually. Surveillance cultures of either expectorated sputum or oropharyngeal cough swabs are recommended at each visit, including nontuberculosis mycobacterium at least annually. Spirometry should also be performed at each visit for patients old enough to reliably perform testing.

Management of PCD Pulmonary Disease

Similar to monitoring, treatment recommendations for PCD patients are largely based on other patient populations because clinical evidence for PCD is limited primarily to case reports and series and very few clinical trials. For patients with PCD, airway clearance using daily chest physiotherapy is highly recommended. The optimal technique to use is still unknown because only one trial to date has compared high-frequency chest-wall oscillation with postural drainage percussion and vibrations (Gokdemir 2014). Based on the absence or dysfunction of ciliary beat in these patients, it is reasonable to consider either autogenic drainage or active cycle of breathing techniques to mobilize mucus from small to larger airways (Schofield 2018). Oscillatory positive expiratory pressure devices are also reasonable to consider because they provide oscillatory frequencies similar to normal cilia.

Evidence also suggests that aerobic exercise may be beneficial in PCD patients for the clearance of secretions

and bronchodilation. One study evaluated the effects of exercise compared with 200 mcg of salbutamol in 12 pediatric patients ages 7 to 15 years; most patients (83%) had a better bronchodilator response to exercise than to salbutamol (Phillips 1998). Another study found increased exercise capacity in PCD patients versus controls, which was most significant in patients with FEV₁ less than 85% (Valerio 2012).

Evidence is conflicting for the use of inhaled bronchodilators in PCD patients. One study demonstrated significant lung function improvement with a single dose of salbutamol 200 mcg, whereas another study did not show a change in lung function after six months of regular salbutamol, dosed at 2 administrations of 100 mcg four times daily (Koh 2000, Hellinckx 1998). It is reasonable, however, to consider the use of bronchodilators before other medications to minimize airway irritation, reduce adverse effects, and improve tolerability.

Hypertonic saline 7% nebulization solution has been evaluated in a meta-analysis in non-CF bronchiectasis, with unclear findings for long-term benefits (Tarrant 2017). A recent randomized controlled trial evaluated the effects of inhaled hypertonic saline on quality of life in PCD patients (Paff 2017). This study found no improvement in the St. George's Respiratory Questionnaire score, but demonstrated significant improvement on the secondary health perception scale (Quality of Life Questionnaire-Bronchiectasis). Based on this evidence, it is reasonable to consider hypertonic saline on a case-by-case basis in this patient population.

Dornase alfa is another mucolytic therapy often used in other patient populations such as CF. Although no PCD-specific trials exist for this drug, a large study of dornase alfa in patients with non-CF bronchiectasis demonstrated more rapid FEV₁ decline and increased frequency of pulmonary exacerbations in patients who received dornase alfa compared with placebo (O'Donnell 1998). This result was thought to occur either because patients with non-CF bronchiectasis do not have high concentrations of DNA in their sputum or because patients with bronchiectasis are typically older and less able to tolerate thinned secretions, causing these secretions to move distally into the airways and lung parenchyma versus being expectorated. In the absence of additional literature, dornase alfa is currently not recommended for routine use in PCD patients.

In addition to inhaled therapies, chronic azithromycin has been shown to decrease airway inflammation. The EMBRACE (Exacerbations in Non-Cystic Fibrosis Bronchiectasis) trial evaluated azithromycin 500 mg three times weekly in adult patients with idiopathic bronchiectasis; in addition, the BAT (bronchiectasis and long-term azithromycin treatment) trial examined azithromycin 250 mg daily in a similar patient population (Altenburg 2013, Wong 2012). These studies found that azithromycin reduced the exacerbation frequency in patients with at least one exacerbation (EMBRACE) and three exacerbations (BAT) in the previous year. In addition, azithromycin was shown to decrease bronchial hyperresponsiveness

and airway neutrophils in pediatric asthma patients; in CF patients, oral azithromycin was shown to reduce inflammatory markers in patients not infected with *Pseudomonas aeruginosa* (Ratjen 2012, Piacentini 2007). An ongoing study in this population is the The BESTCILA (better experimental screening and treatment for primary ciliary dyskinesia) trial, which is a European multi-center, double-blind, randomized, placebo-controlled, parallel group study of azithromycin 250 mg (for patients who weigh less than 40 kg [88.2 lb]) or 500 mg (for patients who weigh 40 kg or more) three times weekly in PCD patients age 7 to 50 years (Kobbernagel 2016). It is important to ensure annual screening for nontuberculous mycobacterium infection before initiation of chronic macrolide therapy.

PCD Respiratory Infections

Because of the impaired mucus clearance, PCD patients are at increased risk of pulmonary infections. However, the most common organisms isolated from PCD respiratory infections are different from those with CF. *Haemophilus influenzae* is the most commonly isolated organism, with reported prevalence of 32%–65% in pediatric patients (Wijers 2017). Other common organisms seen in patients with PCD include *Streptococcus pneumoniae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, *Achromobacter xylosoxidans*, *Burkholderia* spp., and nontuberculous mycobacteria.

In the absence of literature suggesting a need for altered dosing in PCD patients, it is reasonable to use normal pediatric dosing of antimicrobial agents to target likely and/or historical organisms for treatment of pulmonary infections. In the absence of previously positive cultures, appropriate oral treatment options include amoxicillin/clavulanic acid or a second- or third-generation cephalosporin, which target the most likely organisms. However, for patients with previously positive respiratory cultures, the antimicrobial regimen selected should target those organisms. For *S. pneumoniae* that is penicillin-resistant, a fluoroquinolone should be considered. For methicillin-resistant *S. aureus*, sulfamethoxazole/trimethoprim, a tetracycline such as doxycycline or minocycline, and linezolid are available oral treatment options. For infection with *A. xylosoxidans*, which is typically resistant, few oral treatment options are available, but oral sulfamethoxazole/trimethoprim can be used. For other organisms, such as *Burkholderia* spp. and nontuberculous mycobacterium, treatment typically includes several agents.

Pseudomonas aeruginosa is seen in about 10% of patients with PCD, with prevalence increasing with age. Patients colonized with *P. aeruginosa* have been shown to have poorer lung function than other patients, but the rate of pulmonary function decline was similar regardless of *Pseudomonas* colonization (Cohen-Cymerknoh 2017).

Given the absence of literature to direct treatment of pulmonary exacerbations in PCD patients, it is reasonable to follow treatment recommendations for other patient

populations such as CF, including empiric treatment for *P. aeruginosa*. Sputum cultures and sensitivities should be used to guide antimicrobial selection, and therapeutic drug monitoring used as appropriate to ensure efficacy and minimize toxicity. A recent case report of a 10-year old patient with PCD who received extended interval tobramycin highlights the need for therapeutic drug monitoring in patients receiving aminoglycosides (Higgins 2018). In this case, the patient required higher than normal doses of tobramycin (12.8 mg/kg once daily) to achieve therapeutic peak concentrations of 20–30 mcg/mL and AUC_{0–24 hours} of 80–110 (mg x hour)/L for treatment of *P. aeruginosa*. Although this finding is based on a solitary case report, it is reasonable to consider that PCD patients may have higher dosing requirements, and therapeutic drug monitoring should be used to optimize dosing.

Inhaled tobramycin therapy may be considered in patients with PCD who are chronically colonized with *P. aeruginosa*. Although no PCD-specific literature exists, inhaled tobramycin 300 mg twice daily, studied for durations of four weeks and six months, has been shown to be beneficial in adult patients with non-CF bronchiectasis. Other inhaled therapies, including aztreonam and colistin, have less clear benefit, and should be considered on a case-by-case basis for patients who are intolerant to tobramycin or for whom this drug has failed. Inhaled ciprofloxacin was shown to reduce total bacterial load and extend the time to exacerbation in two phase II trials; however, this therapy is not yet commercially available (Daniels 2016).

For patients with PCD who also have associated asthma or airway reactivity, it is reasonable to consider inhaled corticosteroids or other therapies in accordance with national asthma guidelines. However, based on available evidence in patients with non-CF bronchiectasis, inhaled corticosteroids should not be routinely used in PCD patients without asthma (Goyal 2014).

Management of PCD Non-Pulmonary Disease

In addition to pulmonary disease, most patients with PCD have chronic rhinosinusitis. Symptoms can vary in severity, but may include a decreased sense of smell, pain, nasal obstruction, and nasal discharge. Abnormal sinus development and nasal polyps are seen in more than 50% of adults with PCD. Treatment is primarily based on symptom relief and is similar to what is used in the general population. Daily sinus irrigation with saline is efficacious in non-PCD patients with rhinosinusitis; given the minimal adverse effect profile, it is reasonable to extrapolate that use to a PCD population. Topical nasal steroids may be considered on a case-by-case basis. Although efficacious in the general population, these steroids have no clear effect on CF patients with nasal polyps, which is thought to be secondary to the neutrophil predominance in CF airways (Beer 2015, Burgel 2004). Similarly, these steroids may not be of significant benefit for PCD patients because of neutrophil predominance. Antibiotic use can be

considered similar to the general population for acute sinusitis, and endoscopic sinus surgery can be considered. Limited evidence suggests that endoscopic sinus surgery provides subjective benefit and may also help to eradicate pathogenic sinus bacteria, potentially providing protection to the lower airways (Lucas 2017a).

Almost all children with PCD experience otologic manifestations of their disease, which may include recurrent acute otitis media, otitis media with effusion, and chronic otitis media. Similar to the general population, these episodes begin between ages 2 and 3 years, but often continue in this population until ages 6 to 8 years and can persist into adulthood. Similar to the general population, oral antibiotics should be used in cases of acute otitis media, targeting common pathogens such as *Streptococcus pyogenes*, *S. aureus*, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* according to the American Academy of Pediatrics guideline for treatment of otitis media (Lieberthal 2013). For patients who are refractory to oral antibiotics, defined as three or more acute otitis media episodes in six months or four or more episodes in the past 12 months, a myringotomy can be considered to obtain middle ear fluid for culture.

Although commonly used in the general population for persistent bilateral otitis media with effusion, pressure equalization tubes (PET) are controversial in children with PCD. The European Respiratory Society Consensus Statement recommends against the use of this intervention in PCD patients, whereas the North American PCD Consensus Recommendations are in favor of the use of these tubes. The primary concern with tube insertion is that mucopurulent ear drainage, which can result in an increased risk of infection, has been described in significantly more PCD patients than those in the general population (30% vs. less than 5%, respectively). However, the benefit of PET has been demonstrated in several studies in which hearing normalized in 80%–100% of patients post-PET placement, and a study of tube-placement versus medical management demonstrated that patients with PET had significant hearing improvements (Shapiro 2016).

Given the potential for early hearing recovery and its implications on speech development, PET tubes should be considered in PCD patients with recurrent otitis media with effusion if they have hearing deficits or speech delays. For patients who experience post-operative otorrhea, topical antibiotic therapies can be considered. A Cochrane review found some evidence in the general population that antibiotic eardrops, including ciprofloxacin, ofloxacin, and gentamicin, were more effective than oral antibiotics, corticosteroid eardrops, and no treatment in patients with otorrhea after PET placement, but did not find a difference when the antibiotic eardrops were combined with a corticosteroid (Syed 2013). Patients should be followed closely by an otolaryngologist for treatment of complications from PET placement, and may also require referral to an audiologist for hearing aids.

DIFFUSE LUNG DISEASES

Childhood interstitial lung disease (chILD) includes a number of heterogeneous disorders that feature remodeling of the lung interstitium and distal airspaces, resulting in abnormal gas exchange. Because not all chILD disorders affect the interstitium, the more all-encompassing term *diffuse lung diseases (DLD)* is now often used in place of chILD. These disorders are extremely rare, with estimated prevalence between 0.13 and 16 patients per 100,000 people worldwide and overall mortality of 6%–30% (Hime 2015).

Common features of DLD include tachypnea, hypoxemia, crackles on auscultation, and cough; some children may also present with wheezing and failure to thrive. ChILD syndrome, a phenotype in infant (younger than 2 years) that requires further diagnostic evaluation, has been defined as having at least three of the four following criteria: (1) *respiratory symptoms* (cough, rapid and/or difficult breathing, or exercise intolerance); (2) *respiratory signs* (resting tachypnea, retractions, digital clubbing, failure to thrive, or respiratory failure); (3) *hypoxemia*; and (4) *diffuse abnormalities on chest radiography or CT scan* (Kurkland 2013). Of interest, common causes of DLD should be excluded, such as CF, immunodeficiency, congenital heart disease, bronchopulmonary dysplasia, and PCD, to name a few.

In 2013, the American Thoracic Society released a clinical practice guideline for chILD (Kurkland 2013). In this guideline, a classification scheme was included, originally published by the chILD Research Network for pediatric DLD, which lists disorders commonly identified during infancy (Table 1). This guideline also includes recommendations for diagnostic imaging and testing, including bronchoscopy with bronchoalveolar lavage and lung biopsy for definitive diagnosis, using video-assisted thoracoscopy rather than open thoracotomy, if possible. In addition, specific subsets of patients should receive additional genetic testing to rule out specific diseases. Newborns with chILD syndrome and severe or rapidly progressive disease should receive testing for genetic abnormalities associated with neonatal DLD, including mutations in *SFTPB*, *SFTPC*, and *ABCA3*, which result in surfactant deficiency disorders. Newborns presenting with chILD syndrome, congenital hypothyroidism, and hypotonia should be tested for mutations or deletions in *NKX2.1*. Finally, those with chILD syndrome leading to respiratory failure and refractory pulmonary hypertension should receive testing for *FOXF1* deletions or mutations.

Shortly after these American Thoracic Society guidelines were published, the European Union chILD collaboration published European protocols for the diagnosis and treatment of chILD (Bush 2015). Although similar in many aspects, the European protocols do offer a few resources not found in the American Thoracic Society guidelines. Specifically, the European group suggests a staging classification for the severity of chILD. This staging scores patients from 1 to 5, with increasing scores indicating increasing

severity, and accounts for the presence or absence of symptoms, hypoxemia less than 90% at rest and during sleep or exercise, and the presence or absence of pulmonary hypertension. In addition, the European group offers some recommendations for dosing of commonly used medications in chILD, including corticosteroids, hydroxychloroquine, and azithromycin, and gives recommendations based on the patient's ventilation status. These recommendations are discussed in detail within the diagnosis-specific sections (pulmonary alveolar proteinosis, surfactant deficiencies, alveolar hemorrhage, and pulmonary vasculitis) later in this chapter.

Although some emerging treatments may have promise in DLD, supportive care continues to be an important focus in this patient population. Patients should have routine pulse oximetry monitoring to determine the need for supplemental oxygen during the day and/or night, during exercise, and during feeding for infants. Although not specifically studied in chILD syndrome, evidence in bronchopulmonary dysplasia and CF suggests that nutritional supplementation may be beneficial. Patients with DLD should avoid environmental exposures, such as secondhand smoke, and will benefit from the pneumococcal vaccine, annual influenza vaccine, and routine childhood immunizations. The exception to this approach is for patients who are immunosuppressed, who should not receive live virus vaccines. Palivizumab is also recommended in appropriate-age chILD patients who have significant respiratory compromise, despite no studies specifically addressing this patient population to confirm the theoretical benefits.

Pulmonary Alveolar Proteinosis

Pulmonary alveolar proteinosis (PAP) is a rare disorder that is defined by accumulation of pulmonary surfactant in the alveolar space resulting from impaired surfactant production and/or metabolism. Prevalence is low, ranging from 3.7 to 6.2 cases per million, and the disease is more common in the male population, with a male-to-female ratio of 2.1–2.7:1 (Griese 2017). Depending on the underlying cause, PAP can present with slowly increasing dyspnea and dry cough, but patients may also have fever, weight loss, fatigue, and chest pain. In addition, neonatal patients with altered surfactant production may present with respiratory distress syndrome or pulmonary hypertension.

Diagnosis of PAP is multifactorial. On chest radiography, patients with PAP have bilateral alveolar infiltrates. Spirometry in patients old enough to perform pulmonary function testing may reveal a restrictive pattern with small lung volume. Chest CT shows a *crazy-paving pattern*, which is a combination of ground-glass opacity and a superimposed reticular pattern that is characteristic to PAP. Lactate dehydrogenase is elevated in 82% of patients with autoimmune PAP, and these patients are also likely to have autoantibodies against granulocyte-macrophage colony-stimulating factor (GM-CSF).

Table 1. Classification Scheme for Pediatric Diffuse Lung Diseases

Disorders More Prevalent in Infancy	
Diffuse developmental disorders	Acinar dysplasia
	Congenital alveolar dysplasia
	Alveolar capillary dysplasia with pulmonary vein misalignment
Growth abnormalities	Pulmonary hypoplasia
	Chronic neonatal lung disease
	Structural pulmonary changes with chromosomal abnormalities
	Associated with congenital heart disease in chromosomally normal children
Specific conditions of undefined etiology	Pulmonary interstitial glycogenosis
	Neuroendocrine cell hyperplasia of infancy
Surfactant dysfunction mutations and related disorders	<i>SPFTB</i> genetic mutations
	<i>SPFTC</i> genetic mutations
	<i>ABCA3</i> genetic mutations
	Other disorders with history consistent with surfactant dysfunction disorder without a yet-recognized genetic disorder
Disorders Not Associated With Infancy	
Disorders of the normal host	Infectious and postinfectious processes
	Aspiration syndromes
	Disorders related to environmental agents
	Eosinophilic pneumonia
Disorders related to systemic disease processes	Immune-related disorders
	Storage disease
	Sarcoidosis
	Langerhans cell histiocytosis
	Malignant infiltrates
Disorders of the immunocompromised host	Opportunistic infection
	Disorders related to therapeutic intervention
	Disorders related to transplantation and rejection syndromes
	Diffuse alveolar damage of unknown etiology
Disorders masquerading as interstitial lung disease	Arterial hypertensive vasculopathy
	Congestive vasculopathy, including veno-occlusive disease
	Lymphatic disorders
	Congestive changes related to cardiac dysfunction

The risk of PAP is increased in patients with GM-CSF antibody concentration greater than 5 mcg/mL (Sakagami 2010). Genetic testing for mutations in genes linked to PAP should also be performed, with the genes to be tested dependent on the age at presentation. Ultimately, bronchoscopy with lavage and either transbronchial or lung biopsy are required to confirm the diagnosis of PAP.

Whole lung lavage (WLL) continues to be the current standard of care for PAP, and can be performed with either bilateral sequential or simultaneous technique. This approach to lavage allows for physical removal of proteinaceous material and local GM-CSF antibodies, which ultimately restores function to alveolar macrophages. This procedure is indicated in patients with symptomatic disease that limits activity,

impaired weight gain, or abnormal lung function. Thresholds that are used at some centers include PaO₂ less than 65 mm Hg, P(A-a)O₂ gradient greater than 40 mm Hg, and a shunt fraction greater than 10%–12%. It is important to note that WLL is not a definitive treatment, with patients requiring repeat treatment often for symptom relief. The median duration of response is 15 months, and 15% of patients will require lavage every 6 months. Extracorporeal membrane oxygenation as a bridge to lung transplantation may be considered in patients with severe hypoxemia that precludes WLL.

In patients with autoimmune PAP, exogenous GM-CSF has been tested as both subcutaneous and aerosolized therapy. A trial of aerosolized GM-CSF in 50 patients showed a response rate of 62%. Dosing regimens are varied, with studies reporting doses of 125 mcg inhaled twice daily every other week, 250 mcg once daily given 4 days on and 4 days off, and 250 mcg twice daily every other week with possible dose escalation to 500 mcg twice daily every other week (Papiris 2014, Wylam 2006, Tazawa 2006). Response to GM-CSF therapy may be delayed because of the time required for precursor cells to be recruited to the lung and differentiated into functional alveolar macrophages by GM-CSF, with response in most patients seen in 4–6 weeks. In this patient population GM-CSF has been used as salvage therapy as well as first-line therapy in lieu of WLL.

Research continues on the optimal treatment of PAP. A 2008 case report detailed the use of GM-CSF in combination with WLL in a patient who did not respond clinically to inhaled GM-CSF alone (Yamamoto 2008). Another approach that has been studied is the use of plasmapheresis in combination with WLL and GM-CSF, but the results from case reports have demonstrated mixed clinical response. Rituximab has also been studied in autoimmune PAP, with several case reports and series published. A 2018 cohort demonstrated clinical improvement in four of 13 patients included after 1 year of treatment (Soyez 2018). In this study, patients received rituximab 1000 mg on days 0 and 14, and three patients each received a third infusion at month 6, 9, and 12, respectively. Other case reports and series have demonstrated improvement with this dosing regimen as well as with rituximab 375 mg/m² weekly for 4 weeks (Kavuru 2011, Amital 2010, Borie 2009). Given this evidence, it may be reasonable to consider this therapy in patients who have disease that is refractory to more standard therapies such as WLL and GM-CSF.

Surfactant Dysfunction

Surfactant dysfunction is a term used to include a number of disorders that result in deficiency of pulmonary surfactant, a complex that reduces surface tension in the lungs and prevents end expiratory atelectasis (Gower 2011). Surfactant protein B (SP-B) deficiency was the first disorder to be recognized, and it is caused by autosomal recessive inheritance of loss-of-function mutation on both *SFTPB* alleles. This deficiency often presents in full-term infants with DLD,

resembling respiratory distress syndrome seen in premature infants. This particular disorder is progressive and fatal, with most patients dying as a result of respiratory failure within 3 months of birth, unless only a partial deficiency is present, which allows for some SP-B production.

Similarly, *ABCA3* mutations can result in severe neonatal lung disease, with patients presenting similarly to those with SP-B deficiency and refractory to available therapies. The *ABCA3* gene is crucial for lamellar body development and also plays a role in transport of surfactant lipids into the lamellar body.

In contrast, surfactant protein C (SP-C) deficiency is inherited in an autosomal dominant pattern or can result from de novo mutations of *SFTPC*, with a single mutation sufficient to cause disease. Presentation can be highly variable, including age of onset and severity of disease.

Mutations on the copy of *NKX2*, including deletions or complete loss-of-function, may also result in severe respiratory distress syndrome. Because this gene is also expressed in the thyroid gland and the central nervous system, congenital hypothyroidism and chorea are often reported in addition to pulmonary dysfunction.

Treatment experience of these disorders, particularly SP-B and *ABCA3* deficiency, is limited because of the poor long-term survival of these patients, and lung transplantation remains one of few therapeutic options. Pulse corticosteroids have been used for treatment of surfactant disorders, and hydroxychloroquine has also been described in case reports for treatment of patients with SP-B, SP-C, and *ABCA3* deficiency.

In a 2017 case report, a 21-month-old boy with homozygous *SFTPB* deficiency was treated with monthly methylprednisolone (30 mg/kg/day for three 3 days), and after 15 months was started on oral hydroxychloroquine (10 mg/kg/day) (Lopez-Andreu 2017). The authors reported that the patient had currently survived to age 8 years, utilizing using supplemental oxygen via by nasal canula, and continuing on both hydroxychloroquine and methylprednisolone as described previously. A case report in a 5-month-old patient with SP-C deficiency used the same dose of hydroxychloroquine; after 1 year the patient gained 6 kg (13.2 lb) and no longer required supplemental oxygen (Rosen 2005). Another case report in an 8-month old boy with SP-C deficiency used a combination of monthly methylprednisolone (30 mg/kg/day for 3 days), oral hydroxychloroquine dosed at 5 mg/kg/day, and added azithromycin 10 mg/kg every other day (Arikan-Ayyildiz 2013). After 1 year on this combination, ventilation support was discontinued and the patient was continued on supplemental oxygen.

An additional case report described a term infant treated with oral corticosteroids and supplemental oxygen who was started on hydroxychloroquine 6 mg/kg/day (Williamson 2013). With the exception of a 6-month discontinuation to allow for vaccination, the patient continued therapy for 11 years, and was finally received a diagnosis of *ABCA3*

deficiency at age 13 years. Her respiratory function remained stable throughout the treatment period, with the exception of a significant decrease in FEV₁ (from 42.2% to 17.6%) while withholding hydroxychloroquine therapy (that returned to baseline after restarting therapy). Of interest, the authors note that, despite long-term hydroxychloroquine therapy, the patient had no significant adverse effects, such as visual disturbances or declines in renal function, and only experienced an intermittent elevation in liver function tests.

Alveolar Hemorrhage

Diffuse alveolar hemorrhage (DAH), which occurs as a result of injury to the small vessels of pulmonary circulation, is typically divided into groups with and without pulmonary capillaritis. The causes without pulmonary capillaritis can be further subdivided into those with and without a cardiovascular cause (Box 1).

Diffuse alveolar hemorrhage can present in many ways, but hallmark signs and symptoms include dyspnea, hemoptysis, anemia, and hypoxia (Martinez-Martinez 2017). On chest

radiography, patients will have ground-glass diffuse opacities and/or consolidation. Patients should have bronchoscopy with bronchoalveolar lavage performed, and the presence of greater than 5% hemosiderin-laden macrophages is highly suggestive of alveolar hemorrhage associated with autoimmune disease. Although definitive diagnosis can be challenging, de Prost and colleagues described a scoring system in 2013 to differentiate DAH based on autoimmune and non-autoimmune causes (de Prost 2013). The retrospective review found that patients with more than 4 of 10 points have an area under the receiver operating curve of 0.95 in favor of autoimmune diseases, indicating good discrimination between patients with immune and non-immune DAH. Although this scoring system has not been validated in a larger population, it may be a useful tool for clinicians.

Treatment of DAH can be divided into acute and chronic management, although the two approaches to management overlap. For acute onset DAH, the focus should be on stabilization and suppression of active disease. Systemic corticosteroids are a mainstay of management, most commonly oral prednisolone, oral prednisone, and intravenous methylprednisolone (Casey 2017). Oral prednisolone or prednisone is typically given at a dose of 1 to 2 mg/kg/day, with the duration determined by response. Intravenous methylprednisolone is typically reserved for more severe disease and exacerbations at doses of 10 to 30 mg/kg/day for 3 to 5 consecutive days, with patients then transitioned to a lower oral prednisone/prednisolone dose and tapered as appropriate (Li 2017). This methylprednisolone dosing (10 to 30 mg/kg/day) has also been used, with doses given 3 days per month to reduce the adverse effects associated with chronic oral corticosteroid therapy. Patients on chronic corticosteroids should be monitored for adverse effects associated with long-term use, including hypertension, hyperglycemia, impaired growth, low bone density, ophthalmologic complications, and adrenal suppression.

In addition to corticosteroids, acute management of DAH may include respiratory support, ranging from oxygen supplementation to mechanical ventilation with high positive end-expiratory pressure (PEEP) (Park 2016). A tamponade effect caused by PEEP can limit capillary bleeding. Coagulation defects should be corrected, with commonly accepted targets of platelets more than 50,000/mm³ and a prothrombin time/international normalized ratio less than 1.5. Agents used to correct these defects may include platelet transfusions, vitamin K, cryoprecipitates, and fresh frozen plasma.

Antifibrinolytics, such as tranexamic acid and aminocaproic acid, can also be considered for acute management of DAH. A case series of tranexamic acid in six patients with hemoptysis, either secondary to bronchoscopy biopsy or spontaneous bleeding secondary to an underlying condition, demonstrated 100% cessation of bleeding after one dose of tranexamic acid without adverse effects. For the two patients who bled during bronchoscopy, a dose of 500 mg/5 mL was

Box 1. Classification Scheme for Pediatric Alveolar Hemorrhage Syndromes

Disorders with Pulmonary Capillaritis

- Idiopathic pulmonary capillaritis
- Wegener granulomatosis
- Microscopic polyangiitis
- Systemic lupus erythematosus
- Goodpasture syndrome
- Antiphospholipid antibody syndrome
- Henoch-Schönlein purpura
- IgA nephropathy
- Polyarteritis nodosa
- Behçet syndrome
- Cryoglobulinemia
- Drug-induced capillaritis
- Idiopathic pulmonary-renal syndrome

Disorders Without Pulmonary Capillaritis

Noncardiovascular causes

- Idiopathic pulmonary hemosiderosis
- Heiner syndrome
- Acute idiopathic pulmonary hemorrhage of infancy
- Bone marrow transplantation
- Immunodeficiency
- Coagulation disorders
- Celiac disease
- Infanticide

Cardiovascular causes

- Mitral stenosis
- Pulmonary veno-occlusive disease
- Arteriovenous malformations
- Pulmonary lymphangioliomyomatosis
- Pulmonary hypertension
- Pulmonary capillary hemangiomas
- Chronic heart failure
- Vascular thrombosis with infarction

administered through the bronchoscope, and the other four patients (spontaneous bleeding) received 500 mg/5 mL tranexamic acid aerosolized three to four times daily (Solomonov 2009). For patients who received aerosolized therapy, this was continued for a range of 2 days up to 3 months. Although no data exist for use in autoimmune conditions, two case series in adult patients post-hematopoietic stem cell transplantation suggest that aminocaproic acid 1000 mg intravenously every 6 hours may also be used for patients with DAH, either alone or in conjunction with corticosteroids (Wanko 2006).

Recombinant factor VIIa (rFVIIa) has been successfully used in patients with DAH, both immune- and non-immune-mediated, by intravenous and bronchoscopic routes (Park 2016). Mechanistically, rFVIIa promotes hemostasis by activating factors IX and X, which subsequently results in fibrin formation at the site of injury. Systemic doses in case reports range from 35–200 mcg/kg, either as single doses or repeated every two to four hours, and intrapulmonary doses range from 50–90 mcg/kg diluted in normal saline and administered as either a single dose or repeated every 24 hours if bleeding continues. The higher systemic

dose can be explained by the separation of alveolar and systemic compartments of the lungs, meaning that a higher systemic concentration is needed to affect receptors in the alveolar compartment. The primary adverse effect is thromboembolic complications, which have rarely been reported in the literature. It is recommended that patients maintain adequate antithrombin III levels to avoid this complication. In contrast, intrapulmonary administration has a lower risk of systemic adverse effects, and is therefore the preferred route of administration.

In pediatric patients, is important to remember that rFVIIa has been shown to have a shorter half-life and more rapid clearance than in adults, which may necessitate higher and more frequent dosing, particularly in neonates and infants younger than 1 year. However, given the increased risk for thromboembolism and the typically poor response to rFVIIa in infants younger than 1 year, it is recommended to avoid rFVIIa therapy if possible.

Chronic management may include corticosteroids and other agents used in acute management, but should also focus on the underlying disease process, as addressed in the next section.

Patient Care Scenario

A 10-year-old boy (height 56 in, weight 34 kg [75 lb]) is seen in clinic for evaluation for possible PCD. He has a consistent wet, productive cough, as well as nasal congestion.

His medical history includes recurrent ear infections during his childhood, for which he received antibiotics and eventually PET. His home drugs include fluticasone

ANSWER

Unfortunately, evidence in PCD patients is extremely limited with few randomized controlled trials, so most evidence is adopted from other disease states, including cystic fibrosis (CF) and non-CF bronchiectasis. Exercise should be encouraged for airway clearance based on evidence in a small patient population that it may provide better bronchodilator response than a short-acting bronchodilator. Albuterol, a short-acting bronchodilator, can be considered before other therapies that may be potentially irritating to the airway, but otherwise would be recommended in a patient with concurrent asthma. Hypertonic saline should be considered, given its benefit in patient-perceived health. Commercially available 3% or 7% saline can be used, and patients should complete post-medication pulmonary function testing to ensure that the medication is tolerated. Dornase alfa

nasal spray (1 spray each nostril once daily), and a daily multivitamin.

After confirmatory genetic and diagnostic nasal nitric oxide testing, PCD is diagnosed. What medication(s) are best to recommend for this patient's airway clearance/pulmonary regimen?

should not be used, based on the available studies in non-CF bronchiectasis that suggested patients had more rapid FEV₁ decline and increased frequency of pulmonary exacerbations.

Although not an inhaled therapy, chronic azithromycin should be considered as well for reduction in airway inflammation. Based on available literature in adult patients with bronchiectasis, it is reasonable to consider initiation of this if the patient continues to be symptomatic. An ongoing multicenter study of azithromycin use in PCD patients, using a dose of 250 mg or 500 mg three times weekly based on body weight (less than 40 kg [88.2 lb] or 40 kg and more, respectively), will hopefully provide clarification on the use of this medication in this specific patient population.

1. Paff T, Daniels JMA, Weersink EL, et al. A randomised controlled trial on the effect of hypertonic saline on quality of life in primary ciliary dyskinesia. *Eur Respir J* 2017;49:1601770.
2. O'Donnell AE, Barker AF, Ilowite JS, et al. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. *rhDNase Study Group. Chest* 1998;113:1329-34.
3. Shapiro AJ, Zariwala MA, Ferkol T, et al. Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD Foundation consensus recommendations based on state of the art review. *Pediatr Pulmonol* 2016;51:115-32.

Pulmonary Vasculitis

Pulmonary vasculitis is a broad category encompassing many diseases, including some of those mentioned previously in the alveolar hemorrhage section. Pulmonary vasculitides are classified according to vessel size affected, with pulmonary involvement most commonly seen in small vessel disease. Table 2 includes the classification for common childhood vasculitis based on the consensus criteria endorsed by the European League Against Rheumatism and the Pediatric Rheumatology European Society (Ozen 2006).

Pulmonary vasculitides often present with systemic manifestations, including malaise, fever, weight loss, joint pain, kidney disease, and rash, as well as DAH (O'Sullivan 2012). In addition, each disease process has its own hallmark presentation. Henoch-Schönlein purpura typically presents with erythematous papules that progress to palpable purpura in the lower extremities, trunk, and face; Wegner granulomatosis presents with the triad of upper and lower airway and renal involvement; and microscopic polyangiitis is always associated with focal segmental necrotizing glomerulonephritis. These disorders all include antineutrophil cytoplasmic antibody (ANCA) positivity in their diagnostic work-up. For patients with isolated DAH but without ANCA positivity, a diagnosis of idiopathic pulmonary hemosiderosis is commonly given.

For induction of remission, the historical treatment has been a combination of cyclophosphamide and corticosteroids;

however, more recent evidence suggests that rituximab can be used in place of cyclophosphamide with similar, if not improved, efficacy. The RAVE (Rituximab in ANCA-Associated Vasculitis) study compared rituximab 375 mg/m² weekly for 4 weeks versus cyclophosphamide 2 mg/kg/day, in addition to corticosteroids, in 197 adult patients with ANCA-positive vasculitis (Stone 2010). Patients who received cyclophosphamide and achieved remission between 3 and 6 months were able to switch to azathioprine (2 mg/kg/day), and patients in the rituximab group who achieved remission were changed from placebo cyclophosphamide to placebo azathioprine. The study found that rituximab was non-inferior to cyclophosphamide for the primary end point, remission of disease without the use of prednisone at 6 months, with 64% of patients in the rituximab group and 53% of patients in the cyclophosphamide group reaching the primary end point ($p < 0.001$). In addition, rituximab was more effective in patients with relapsing disease, with 67% of rituximab patients versus 42% of cyclophosphamide patients with relapsing disease reaching the primary end point ($p = 0.01$). Based on this evidence, rituximab can be considered in place of cyclophosphamide, given its equivalent efficacy and improved adverse effect profile.

In a follow-up study of the original RAVE patients, rituximab induction was shown to be more effective than conventional immunosuppression (cyclophosphamide and azathioprine) at 6 and 12 months, with equivalent efficacy by 18 months as a result of reconstituted B cells (Specks 2013).

Table 2. Childhood Vasculitis Classification

Predominantly large-vessel vasculitis	Takayasu arteritis
Predominantly medium-size vessel vasculitis	Kawasaki disease
	Childhood polyarteritis nodosa
	Cutaneous polyarteritis
Predominantly small-vessels vasculitis	Granulomatous
	• Wegener granulomatosis
	• Churg-Strauss syndrome
	Non-granulomatous
	• Henoch-Schönlein purpura
	• Microscopic polyangiitis
	• Isolated cutaneous leukocytoclastic vasculitis
• Hypocomplementemic urticarial vasculitis	
• Goodpasture syndrome	
Other vasculitides	Behçet disease
	Vasculitis secondary to infection, malignancies, and drugs
	Vasculitis associated with connective tissue diseases
	Isolated vasculitis of the CNS
	Cogan syndrome
	Unclassified

In 2014, the RAVE authors published data demonstrating that the same regimen, rituximab plus corticosteroids, was effective in treatment of these patients who relapsed, regardless of their previous induction regimen (Miloslavsky 2014).

When possible, steroid-sparing agents should be considered for long-term management of vasculitis, although corticosteroids may be used in combination for acute management. Therapeutic options include hydroxychloroquine, calcineurin inhibitors, antiproliferative agents, mechanistic target of rapamycin inhibitors, and biologics.

Use of hydroxychloroquine has been reported in many patient populations with vasculitis with mixed results, although recently it has fallen out of favor. Dosing is 5 mg/kg/day of actual body weight, based on the recommendation from the American Academy of Ophthalmology to mitigate potential for retinal toxicity, with improvement expected 1 to 3 months after starting therapy (Marmor 2016). Hydroxychloroquine can be used as monotherapy or as adjunctive therapy to steroids or other agents. Before initiation of hydroxychloroquine, patients should have an ophthalmic examination and then annual assessments while being treated because of the potential for retinal toxicity leading to irreversible retinopathy.

Azathioprine and methotrexate have been used historically for maintenance therapy. A 2008 French study compared use of these two agents (azathioprine 2 mg/kg/day vs. methotrexate 0.3 mg/kg/week increased progressively to 25 mg/week) for 12 months, and found similar relapse rates (36% vs. 33%, respectively) (Pagnoux 2008). Methotrexate was associated with more adverse effects, contributing to evidence suggesting that azathioprine is preferred for maintenance therapy.

In 2015, a single center published their experience with using rituximab versus azathioprine for maintenance of remission (Guillevin 2014). Patients in the rituximab group received 500 mg of rituximab on days 0 and 14 and at months 6, 12, and 18, and patients in the azathioprine group received azathioprine 2 mg/kg/day until month 22. More patients in the rituximab group had sustained remission at month 28 versus those in the azathioprine group (95% vs. 71%, respectively; hazard ratio for relapse 6.61; $p=0.002$). Based on the results of this trial, it is reasonable to use rituximab for induction and maintenance of remission versus daily oral azathioprine therapy.

More recently, the French Vasculitis Study Group published the results of their trial (MAINRITSAN2) comparing individually tailored versus fixed-schedule rituximab for remission maintenance in patients with ANCA-associated vasculitis (Charles 2018). Patients in the tailored group received 500 mg rituximab at the start of the trial and then not again until CD19⁺B lymphocytes or ANCA had reappeared or the ANCA tier rose markedly based on every testing three months until month 18. Patients in the control group received rituximab 500 mg at days 0 and 14 and months 6, 12, and 18. At the end of the 28-month study period, the relapse rates did not differ significantly between the groups (17.3% in the tailored group

Practice Points

In determining the optimal pharmacotherapy for patients with DLD, practitioners should consider the following key points:

- It is important to establish the genetic cause of the condition, as some will respond to particular therapies better than others.
- For patients with PAP, WLL continues to be the standard of care, with aerosolized GM-CSF also showing delayed benefits (4–6 weeks).
- Patients with surfactant dysfunction continue to have few treatment choices; for example, SP-B and ABCA3 deficiency may respond to corticosteroids, and hydroxychloroquine may be considered for these patients as a long-term treatment option.
- Acute management of DAH should include high-dose corticosteroids, supportive care targeted at correcting coagulation defects, and appropriate ventilation. Antifibrinolytics and factor VIIa products have been used with success, both intravenously and by aerosolization, and should be considered based on product availability.
- Rituximab, at either fixed or tailored dosing, should be used for induction and maintenance of remission in patients with pulmonary vasculitis, with azathioprine and hydroxychloroquine representing alternative maintenance options.

vs. 9.9% in the fixed schedule group, $p=0.22$). The tailored infusion group did receive fewer infusions, with a median of three versus five administrations, respectively. Based on this trial, it is reasonable to consider either dosing regimen, with the individualized regimen being most cost-effective based on lower number of administrations.

CONCLUSION

The management of the diseases described in this chapter (PCD and DLD) is complex and continues to evolve as new evidence emerges. Given the rarity of these diagnoses, it is imperative that patients are referred to a center with experience in treating these diseases for the best chance at positive outcomes.

REFERENCES

- Altenburg J, de Graaf CS, Stienstra Y, et al. [Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial](#). JAMA 2013;309:1251-9.
- Amital A, Dux S, Shitrit D, et al. [Therapeutic effectiveness of rituximab in a patient with unresponsive autoimmune pulmonary alveolar proteinosis](#). Thorax 2010;65:1025-6.
- Arikan-Ayyildiz A, CaglayanSozmen S, Isik S, et al. [Survival of an infant with homozygous surfactant protein C \(SFTPC\) mutation](#). Pediatr Pulmonol 2013;49:E112-5.

- Beer H, Southern KW, Swift AC. [Topical nasal steroids for treating nasal polyposis in people with cystic fibrosis \[update\]](#). *Cochrane Database Syst Rev* 2015;6:CD008253.
- Borie R, Debray MP, Laine C, et al. [Rituximab therapy in autoimmune pulmonary alveolar proteinosis](#). *Eur Respir J* 2009;33:1503-6.
- Burgel PR, Cardell LO, Ueki IF, Nadel JA. [Intranasal steroids decrease eosinophils but not mucin expression in nasal polyps](#). *Eur Respir J* 2004;24:594-600.
- Bush A, Cunningham S, de Blic J, et al. [European protocols for the diagnosis and initial treatment of interstitial lung disease in children](#). *Thorax* 2015;70:1078-84.
- Casey AM, Welsh SK. [Interstitial lung disease: management and treatment](#). *Annals Amer Thorac Soc* 2017;14(Suppl 2):S174-5.
- Charles P, Terrier B, Perrodeau E, et al. [Comparison of individually tailored versus fixed-schedule rituximab regimen to maintain ANCA-associated vasculitis remission: results of a multicentre, randomized controlled, phase III trial \(MAINRITSAN2\)](#). *Ann Rheum Dis* 2018;77: 1143-9.
- Cohen-Cyberknoh M, Weigert N, Gileles-Hillel A, et al. [Clinical impact of Pseudomonas aeruginosa colonization in patients with Primary Ciliary Dyskinesia](#). *Respiratory Medicine* 2017;131:241-6.
- Daniels MLA, Noone PG. [Genetics, diagnosis, and future treatment strategies for primary ciliary dyskinesia](#). *Expert Opin Orphan Drugs* 2015;3:31-44.
- de Prost N, Parrot A, Cuquemelle E, Picard C, Cadranel J. [Immune diffuse alveolar hemorrhage: a retrospective assessment of a diagnostic scale](#). *Lung* 2013;191:559-63.
- Gokdemir Y, Karadag-Saygi E, Erdem E, et al. [Comparison of conventional pulmonary rehabilitation and high-frequency chest wall oscillation in primary ciliary dyskinesia](#). *Pediatr Pulmonol* 2014;49:611-6.
- Gower WA, Noguee LM. [Surfactant dysfunction](#). *Paediatr Respir Rev* 2011;12:223-9.
- Goyal V, Chang AB. [Combination inhaled corticosteroids and long-acting beta2-agonists for children and adults with bronchiectasis](#). *Cochrane Database Syst Rev* 2014;6:CD010327.
- Griese M. [Pulmonary alveolar proteinosis: a comprehensive clinical perspective](#). *Pediatrics* 2017;140:e20170610.
- Guillevin L, Pagnoux C, Karras A, et al. [Rituximab versus azathioprine for maintenance in ANCA-associated vasculitis](#). *N Engl J Med* 2014;371:1771-80.
- Hellinckx J, Demedts M, De Boeck K. [Primary ciliary dyskinesia: evolution of pulmonary function](#). *Eur J Pediatr* 1998;157:422-6.
- Higgins KL, Noda C, Stultz JS. [Extended interval tobramycin pharmacokinetics in a pediatric patient with primary ciliary dyskinesia presenting with an acute respiratory exacerbation](#). *J Pediatr Pharmacol Ther* 2018;23:159-63.
- Hime NJ, Zurynski Y, Fitzgerald D, et al. [Childhood interstitial lung disease: a systematic review](#). *Pediatr Pulmonol* 2015;50:1383-92.
- Kavuru MS, Malur A, Marshall I, et al. [An open-label trial of rituximab therapy in pulmonary alveolar proteinosis](#). *Eur Respir J* 2011;38:1361-7.
- Khan A, Agarwal R. [Pulmonary alveolar proteinosis](#). *Resp Care* 2011;56:1016-28.
- Knowles M, Zariwala M, Leigh M. [Primary ciliary dyskinesia](#). *Clin Chest Med* 2016;37:449-61.
- Kobbernagel HE, Buchvald FF, Haarman EG, et al. [Study protocol, rationale and recruitment in a European multi-centre randomized controlled trial to determine the efficacy and safety of azithromycin maintenance therapy for 6 months in primary ciliary dyskinesia](#). *BMC Pulm Med* 2016;16:104.
- Koh YY, Park Y, Jeong JH, Kim CK, Min YG, Chi JG. [The effect of regular salbutamol on lung function and bronchial responsiveness in patients with primary ciliary dyskinesia](#). *Chest* 2000;117:427-33.
- Kurland G, Deterding RR, Hagood JS, et al. [An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy](#). *Am J Respir Crit Care Med* 2013;188:376-94.
- Li YT, Guo YX, Cai LM, et al. [Methylprednisolone pulse therapy rescued life-threatening pulmonary hemorrhage due to idiopathic pulmonary hemosiderosis](#). *Am J Emer Med* 2017;35:1786.e3-e7.
- Lieberthal AS, Carroll AE, Chonmaitree T, et al. [The diagnosis and management of acute otitis media](#). *Pediatrics* 2013;131:e964-99.
- Lopez-Andreu JA, Hidalgo-Santos AD, Fuentes-Castello MA, et al. [Delayed presentation and prolonged survival of a child with surfactant protein B deficiency](#). *J Pediatr* 2017;190:268-70.
- Lucas JS, Alanin MC, Collins, et al. [Clinical care of children with primary ciliary dyskinesia](#). *Expert Review of Respiratory Medicine* 2017a;11:779-90.
- Lucas JS, Barbato A, Collins SA, et al. [European Respiratory Society guidelines for the diagnosis of primary ciliary dyskinesia](#). *Eur Respir J* 2017b;49:161090.
- Marmor ME, Kellner U, Lai TY, et al. [Recommendations on screening for chloroquine and hydroxychloroquine retinopathy \(2016 revision\)](#). *Ophthalmology* 2016;123:1386-94.
- Martinez-Martinez MU, Herera-van Oostdam DA, Abud-Mendoza C. [Diffuse alveolar hemorrhage in autoimmune disease](#). *Curr Rheumatol Rep* 2017;19:27.
- Mullowney T, Manson D, Kim R, Stephens D, Shah V, Dell S. [Primary ciliary dyskinesia and neonatal respiratory distress](#). *Pediatrics* 2014;314:1160-66.
- O'Donnell AE, Barker AF, Ilowite JS, Fick RB. [Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I](#). *rhDNase Study Group*. *Chest* 1998;113:1329-34.

- O'Sullivan BP. [Pulmonary complications of systemic vasculitides](#). *Pediatr Res* 2012;13:37-43.
- Ozen S, Ruperto N, Dillon MJ, et al. [EULAR/PRES endorsed consensus criteria for the classification of childhood vasculitides](#). *Ann Rheum Dis* 2006;65:936-41.
- Paff T, Daniels JMA, Weersink EL, et al. [A randomised controlled trial on the effect of hypertonic saline on quality of life in primary ciliary dyskinesia](#). *Eur Respir J* 2017;49:1601770.
- [Pagnoux C, Mahr A, Hamidou MA, et al. Azathioprine or methotrexate maintenance for ANCA-associated vasculitis](#). *N Engl J Med* 2008;259:2780-803.
- Papiris SA, Tsigotis P, Kolilekas L, et al. [Long-term inhaled granulocyte macrophage-colony-stimulating factor in autoimmune pulmonary alveolar proteinosis: effectiveness, safety, and lowest effective dose](#). *Clin Drug Investig* 2014;34:553-64.
- Park JA. [Diffuse alveolar hemorrhage and recombinant factor VIIa treatment in pediatric patients](#). *Korean J Pediatr* 2016;59:105-13.
- Phillips GE, Thomas S, Heather S, Bush A. [Airway response of children with primary ciliary dyskinesia to exercise and beta2-agonist challenge](#). *Eur Resp J* 1998;11:1389-91.
- Piacentini GL, Peroni DG, Bodini A, et al. [Azithromycin reduces bronchial hyperresponsiveness and neutrophilic airway inflammation in asthma children: a preliminary report](#). *Allergy Asthma Proc* 2007;28:194-8.
- Polineni D, Davis SD, Dell SD. [Treatment recommendations in primary ciliary dyskinesia](#). *Paediatric Respiratory Reviews* 2016;18:39-45.
- Ratjen F, Saiman L, Mayer-Hamblett N, et al. [Effect of azithromycin on systemic markers of inflammation in patients with cystic fibrosis uninfected with *Pseudomonas aeruginosa*](#). *Chest* 2012;142:1259-66.
- Rosen DM, Waltz DA. [Hydroxychloroquine and surfactant protein C deficiency](#). *N Engl J Med* 2005;352:207-8.
- Sakagami T, Beck D, Uchida K, et al. [Patient derived granulocyte/macrophage colony-stimulating factor auto-antibodies reproduce pulmonary alveolar proteinosis in non-human primates](#). *Am J Respir Crit Care Med* 2010;182:49-61.
- Schofield LM, Duff A, Brennan C. [Airway clearance techniques for primary ciliary dyskinesia: is the cystic fibrosis literature portable?](#) *Paediatric Respiratory Reviews* 2018;25:73-7.
- Shah A, Shoemark A, MacNeill SJ, et al. [A longitudinal study characterizing a large adult primary ciliary dyskinesia population](#). *Eur Respir J* (2015);48:441-50.
- Shapiro AJ, Zariwala MA, Ferkol T, et al. [Diagnosis, monitoring, and treatment of primary ciliary dyskinesia: PCD Foundation Consensus recommendations based on state of the art review](#). *Pediatr Pulmonol* 2016;51:115-32.
- Solomonov A, Fruchter O, Zuckerman T, Brenner B, Yigla M. [Pulmonary hemorrhage: a novel mode of therapy](#). *Respir Med* 2009;103:1196-1200.
- Soyez B, Borie R, Menard C, et al. [Rituximab for auto-immune alveolar proteinosis, a real life cohort study](#). *Respir Res* 2018;19:74.
- Specks U, Merkel PA, Seo P, et al. [Efficacy of remission-induction regimens for ANCA-associated vasculitis](#). *N Engl J Med* 2013;369:417-27.
- Stone JH, Merkel PA, Spiera R, et al. [Rituximab versus cyclophosphamide for ANCA-associated vasculitis](#). *N Engl J Med* 2010;363:221-32.
- Susarla SC, Fan LL. [Diffuse alveolar hemorrhage syndromes in children](#). *Curr Opin Pediatr* 2007;19:314-20.
- Syed MI, Suller S, Browning GG, Akeroyd MA. [Interventions for the prevention of postoperative ear discharge after insertion of ventilation tubes in children](#). *Cochrane Database Syst Rev* 2013;30:CD008512.
- Tarrant BJ, Maitre CL, Romero L, et al. [Mucoactive agents for chronic, non-cystic fibrosis lung disease: a systematic review and meta-analysis](#). *Respirology* 2017;22:1084-92.
- Tazawa R, Nakata K, Inoue Y, Nukiwa T. [Granulocyte-macrophage colony-stimulating factor inhalation therapy for patients with idiopathic pulmonary alveolar proteinosis: a pilot study; and long-term treatment with aerosolized granulocyte-macrophage colony-stimulating factor: a case report](#). *Respirology* 2006;11:S61-4.
- Valerio G, Giallauria F, Montella S, et al. [Cardiopulmonary assessment in primary ciliary dyskinesia](#). *Eur J of Clin Invest* 2012;42:617-22.
- Wanko SO, Broadwater G, Folz RJ, Chao NJ. [Diffuse alveolar hemorrhage: retrospective review of clinical outcome in allogeneic transplant recipients treated with aminocaproic acid](#). *Biol Blood Marrow Transplant* 2006;12:949-53.
- Wijers CDM, Chmiel JF, Gaston BM. [Bacterial infections in patients with primary ciliary dyskinesia: Comparison with cystic fibrosis](#). *Chronic Respiratory Disease* 2017;14:392-406.
- Williamson M, Wallis C. [Ten-year follow up of hydroxychloroquine treatment for ABCA3 deficiency](#). *Pediatr Pulmonol* 2013;49:299-301.
- Wong C, Jayaram L, Karalus N, et al. [Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis \(EMBRACE\): a randomized, double-blind, placebo-controlled trial](#). *Lancet* 2012;380:660-7.
- Wylam ME, Ten R, Prakash UBS. [Aerosol granulocyte-macrophage colony-stimulating factor for pulmonary alveolar proteinosis](#). *Eur Respir J* 2006;27:585-93.
- Yamamoto H, Yamaguchi E, Agata H, et al. [A combination therapy of whole lung lavage and GM-CSF inhalation in pulmonary alveolar proteinosis](#). *Pediatr Pulmonol* 2008;43:828-30.

Self-Assessment Questions

1. A 6-year-old boy presents to the pulmonary clinic for evaluation and diagnostic work-up. He has a persistent wet cough that his parents say has been present most of his life, a history of numerous episodes of acute otitis media, and consistent complaints of nasal congestion. Additionally, he has situs inversus. Which one of the following is the best initial diagnostic testing to recommend for this patient for primary ciliary dyskinesia (PCD) work-up?
 - A. Ciliary biopsy for electron microscopy; genetic testing
 - B. Nasal nitric oxide measurement only
 - C. Nasal nitric oxide measurement; genetic testing
 - D. Ciliary biopsy for electron microscopy only
 2. A 15-year-old girl with PCD and asthma presents to clinic for regularly scheduled follow-up. Which one of the following is best to recommend for this patient?
 - A. Albuterol and dornase alfa
 - B. Albuterol and hypertonic saline
 - C. Exercise and dornase alfa
 - D. Hypertonic saline and dornase alfa
- Questions 3 and 4 pertain to the following case.**
- J.J. is a 12-year-old boy (weight 40 kg) with PCD who presents to the pulmonary clinic with a drop in his FEV₁ from 86% to 78%. He is afebrile but complains of an increased productive cough and feeling short of breath. A sputum culture is obtained during J.J.'s clinic visit, but results will not be available for 2 days.
3. Which one of the following is best to recommend for J.J. until culture results are available?
 - A. Azithromycin 500 mg on day 1, then 250 mg on days 2-4
 - B. Amoxicillin/clavulanate 875 mg BID for 14 days
 - C. Doxycycline 100 mg BID for 14 days
 - D. Ciprofloxacin 750 mg BID for 14 days
 4. Two days later, J.J.'s culture is finalized, with positive results for *Moraxella catarrhalis* and methicillin-sensitive *Staphylococcus aureus*. Which one of the following is best to recommend for J.J.?
 - A. Amoxicillin/clavulanate and doxycycline
 - B. Ciprofloxacin and sulfamethoxazole/trimethoprim
 - C. Amoxicillin/clavulanate
 - D. Sulfamethoxazole/trimethoprim
5. A 7-year-old boy with PCD has his first *Pseudomonas aeruginosa*-positive sputum culture. Which one of the following is best to recommend for this patient for eradication and treatment?
 - A. Inhaled aztreonam 75 mg TID for 28 days
 - B. Inhaled tobramycin 300 mg BID for 28 days and oral ciprofloxacin 15 mg/kg Q12 hours for 14 days
 - C. Inhaled tobramycin 300 mg BID for 28 days
 - D. Inhaled aztreonam 75 mg TID for 28 days and oral ciprofloxacin 15 mg/kg Q12 hours for 14 days
 6. A 3-year-old girl (weight 11 kg) has a medical history that includes PCD and recurrent otitis media. She presents to clinic for her fourth ear infection this year. The patient has complained of her ear hurting for 2 days, and her temperature at home has been 100–101.3°F. She has previously responded well to oral amoxicillin, and has no pertinent medication allergies. Her most recent course of antibiotics was completed 6 weeks ago. Which one of the following is best to recommend for this patient?
 - A. Amoxicillin 90 mg/kg/day divided BID for 7 days
 - B. Amoxicillin 45 mg/kg/day divided BID for 7 days
 - C. Amoxicillin 90 mg/kg/day divided BID for 7 days and referral to an otolaryngologist for evaluation for PET tubes
 - D. Watchful waiting
 7. A 3-year-old boy with PCD and recurrent otitis media had PET tubes placed 2 weeks ago. Shortly after surgery, his mother calls the office with concerns that the boy is having drainage from his ear. The patient is afebrile and does not complain of pain. Which one of the following is best to recommend for this patient?
 - A. No treatment
 - B. Ofloxacin otic drops 5 drops in each ear BID for 10 days
 - C. Oral amoxicillin 90 mg/kg/day divided BID for 7 days
 - D. Prednisolone otic drops 2 drops in each ear BID for 10 days
 8. Which of the following is part of the staging scoring system for assessing disease severity in patients with childhood interstitial lung disease?
 - A. Presence of congestive heart failure
 - B. Presence of pulmonary hypertension
 - C. Hypoxemia less than 80% at rest
 - D. Hypoxemia less than 80% during sleep or exercise

Questions 9–11 pertain to the following case.

J.Z., a 13-year-old boy with no significant medical history, presents to the ED with dyspnea and new-onset hemoptysis. He is able to talk and answer questions appropriately, but gets short of breath and continues to cough up bloody sputum. His hemoglobin on initial labs is 9.7 g/dL; his oxygen saturation is 94%.

9. Which one of the following is the best first-line therapy to recommend for J.Z.?
- A. IV methylprednisolone 10 mg/kg
 - B. 2 units of packed red blood cells
 - C. Fresh frozen plasma
 - D. Supplemental oxygen
10. One hour later, J.Z.'s hemoglobin is 6.8 g/dL, platelets 70,000/mcl, INR 1.3, and oxygen saturation is 85%. Which one of the following is best to recommend for J.Z.?
- A. Supplemental oxygen and fresh frozen plasma
 - B. Supplemental oxygen and 2 units of packed red blood cells
 - C. Supplemental oxygen and platelet infusion
 - D. 2 units of packed red blood cells
11. Despite these initial interventions, J.Z. continues to decline and requires intubation and mechanical ventilation. Which one of the following is best to recommend for J.Z.?
- A. Intrapulmonary rFVIIa 50 mcg/kg
 - B. Tranexamic acid 250 mg administered via bronchoscopy
 - C. Intrapulmonary rFVIIa 100 mcg/kg
 - D. Intravenous rFVII 25 mcg/kg

Questions 12 and 13 pertain to the following case.

M.P. is a 12-year-old girl with newly diagnosed Wegner's granulomatosis.

12. Which one of the following is best to recommend for induction of remission in M.P.?
- A. Rituximab 375 mg/m² weekly for 4 weeks and prednisone 2 mg/kg/day
 - B. Cyclophosphamide 2 mg/kg/day
 - C. Rituximab 375 mg/m² weekly for 4 weeks
 - D. Cyclophosphamide 2 mg/kg/day and prednisone 2 mg/kg/day

13. M.P. achieves remission. Which one of the following is best to recommend for maintenance of M.P.'s remission?
- A. Azathioprine 2 mg/kg/day
 - B. Prednisone 1 mg/kg/day
 - C. Methotrexate 0.3 mg/kg/week
 - D. Rituximab dosed at days 0 and 14 and months 6, 12, and 18

Questions 14 and 15 pertain to the following case.

G.M. is a 7-year-old boy with ANCA-associated pulmonary vasculitis, now in remission after induction treatment.

14. G.M.'s parents are interested in the differences between an individually tailored versus fixed-schedule rituximab for maintenance of remission. Which of the following is G.M. most likely to benefit from if he receives the individually tailored dosing regimen?
- A. Decreased side effects
 - B. Decreased corticosteroid exposure
 - C. Decreased number of rituximab doses
 - D. Decreased relapse rates
15. Which one of the following appropriately pairs a medication used in maintenance of remission with a common side effect that G.M.'s parents should be counseled on?
- A. Rituximab – mucocutaneous reactions
 - B. Azathioprine – constipation
 - C. Rituximab – hypoglycemia
 - D. Methotrexate – progressive multifocal leukoencephalopathy