ATS Core Curriculum 2017: Part II. Pediatric Pulmonary Medicine

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Severe Asthma in Children: Outpatient Evaluation

Emily Barsky and Jonathan Gaffin

Introduction

Pediatric severe asthma accounts for only 2 to 5% of pediatric asthma cases (1, 2) but a much greater fraction of asthma cost and morbidity (3). The ATS/European Respiratory Society definition of severe asthma is asthma that (1) requires treatment with high-dose inhaled corticosteroids plus a second controller throughout the previous year,

(2) requires treatment with systemic corticosteroids for 50% of the previous year to prevent it from becoming “uncontrolled,” or (3) remains “uncontrolled” despite these therapies (1). Evaluation of such patients must confirm the diagnosis and address modifiable factors contributing to morbidity before escalation of therapy, as outlined in Figure 1. This approach may be best undertaken by a multidisciplinary team consisting of pulmonary and allergy specialists, mental health professionals, nurses, and community resources, including school personnel (4, 5). Adjunct subspecialists, such as otorhinolaryngologists, gastroenterologists, and endocrinologists may be valuable in assessing comorbidities and medication side effects.

Diagnosis Confirmation

Up to 30% of severe asthma referrals are misdiagnosed (6). Masquerading diagnoses include vocal cord dysfunction, central airway obstruction, suppurative lung diseases, and bronchiolitis obliterans. Careful history and examination should elicit clues to alternative diagnoses as well as supporting features of asthma. Spirometry (with inspiratory flow volume loops) with demonstration of bronchodilator reversibility, or consideration of bronchoprovocation testing in the absence of obstruction, is imperative to confirm the diagnosis (1, 7). For atypical presentations, such as rapidly declining

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Figure 1. Proposed algorithm for assessment of severe asthma.

lung function, excessive mucus production, or the absence of atopy, further testing should be performed based on suspected alternative diagnoses. The utility of flexible bronchoscopy is controversial, but it should be considered to evaluate for alternative diagnoses (2). Chest computed tomography (CT) scan is only recommended for atypical presentations (1).

Evaluation for Difficult-to-Treat Asthma

After confirmation of the diagnosis, the next steps are to elicit and address modifiable factors contributing to poor control. Up to 55% of patients with severe asthma ultimately have difficult-to-treat asthma (8)—asthma that can be controlled with appropriate management.

Medication Delivery

Despite self-reports of excellent adherence, fewer than half of patients take 80% of their medications (9). Furthermore, children frequently do not administer inhalers correctly (8) and lack appropriate supervision. Formally assessing medication adherence by objective measures (pharmacy record review, dose counters, and actuation monitoring devices) and repeated review of administration technique are necessary at each visit. Partnering with school nurses to deliver controller medications can be a valuable means to improve adherence.

Environmental Exposures

Assessment of home and school environments for potential triggers starts with careful review of exposures to potential allergens,

environmental smoke, and irritants. A home visit by trained community health professionals should take notice of clutter, dust, tobacco smoke, and toxic inhalants (detergents, unvented gas appliances), pets, and pest infestation. Such exposures contribute directly to patient symptoms (8) and interventions, and education provided at these visits offers measurable improvements in morbidity and healthcare use (10).

Comorbidities

Asthma comorbidities are common and often result in more severe disease. Allergic rhinitis, rhinosinusitis, and obesity are the most prevalent (11). Vitamin D deficiency has been associated with severe asthma and may lead to glucocorticoid insensitivity (12), although it is unclear whether supplementation improves asthma outcomes (13). Gastroesophageal reflux is a common comorbidity (and masquerader); whether it exacerbates asthma is controversial, and treatment of asymptomatic gastroesophageal reflux is not beneficial (14). Psychosocial stressors and psychiatric problems for patient or caregiver affect asthma control in up to 48% of the cases by increased symptom reporting, poor adherence, and potentially increased airway inflammation (15). In addition, allergic bronchopulmonary mycosis; eosinophilic esophagitis; dysfunctional breathing, including hyperventilation and vocal cord dysfunction; and sleep-disordered breathing should be considered. At a minimum, evaluation should include total IgE, specific IgE, or skin prick testing for environmental allergens, and careful assessment of body mass index and sinonasal disease. Further evaluation could include serum vitamin D, complete blood count, and immunoglobulin profile in patients with frequent infections, and dysfunctional breathing assessment.

Assessment of Steroid Responsiveness

After addressing difficult-to-treat asthma, a small proportion emerges truly therapy resistant. At this point, more invasive evaluation to determine steroid responsiveness or asthma phenotypes may be considered. Response to intramuscular triamcinolone acetate or observed oral corticosteroid should be measured by improved symptoms, lung function, and/or markers of airway inflammation, such as fractional exhaled nitric oxide. This may inform decisions regarding whether to escalate steroid therapy or consider alternative therapies (1); up to 20% of children may demonstrate additional improvement with triamcinolone (16, 17). Flexible bronchoscopy is potentially helpful in understanding the inflammatory profile of the airway (18), but outcome data are lacking. Furthermore, recent evidence suggests that airway inflammatory phenotypes, assessed by sputum, are not stable over time and should not guide therapy (19). For patients refractory to inhaled steroid-based therapies, absolute eosinophil counts and total IgE levels will be necessary to determine eligibility for biologic agents. Biologic therapies currently approved by the U.S. Food and Drug Administration are outlined in Table 1.

Conclusions

Outpatient evaluation of children with severe asthma requires confirming the diagnosis and addressing modifiable factors, including medication delivery, environmental exposures, and comorbidities. Those who are resistant to therapy may require more invasive evaluation.

Table 1. U.S. Food and Drug Administration–approved biologic drugs for pediatric severe asthma

Drug	Mechanism of Action	Dosing (Route)	Indication	Clinical Outcomes	Potential Serious Side Effects
Omalizumab (Xolair); FDA approved 2002	Anti-IgE mAb Binds IgE Fc region Prevents binding to mast cells and basophils	150, 225, 300, or 375 mg every 2 wk or every 4 wk (SC)	Age ≥ 6 yr old Moderate-severe asthma and perennial aeroallergen sensitization	↓ Exacerbation frequency ↓Symptoms ↓ ICS dose ↑FEV ₁ ↑QOL	Anaphylaxis (up to 0.2%) Not associated with malignancy in postmarketing safety study (19)
Mepolizumab (Nucala); FDA approved 2015	Anti-IL-5 mAb Inhibits IL-5 binding to α-subunit of IL-5 receptor complex on eosinophils Inhibits growth, differentiation, recruitment, activation, and survival of eosinophils	100 mg every 4 wk (SC)	Age ≥ 12 yr old Severe eosinophilic asthma (blood eosinophil count ≥ 150 cells/μL)	↓ Exacerbation frequency ↓Symptoms ↓ OCS dose ±FEV ₁ ↑QOL	Hypersensitivity reactions Herpes zoster
Reslizumab (Cinqair); FDA approved 2016	Anti-IL-5 mAb Inhibits IL-5 binding to α-subunit of IL-5 receptor complex on eosinophils Inhibits growth, differentiation, recruitment, activation, and survival of eosinophils	3 mg/kg every 4 wk (IV)	Age ≥ 18 yr old Severe eosinophilic asthma (blood eosinophil count ≥ 400 cells/μL)*	↓ Exacerbation frequency ↓Symptoms ↑FEV ₁ ↑QOL	Anaphylaxis (0.3%) Transient ↑CPK Note: 12- to 18-year-old patients had higher rate of exacerbations than placebo

Definition of abbreviations: CPK = creatine phosphokinase; FDA = U.S. Food and Drug Administration; ICS = inhaled corticosteroids; IV = intravenous; mAb = monoclonal antibody; OCS = oral corticosteroids; QOL = quality of life; SC = subcutaneous.

Bold text indicates key clinical findings.

*Phase III trial entry criteria, not part of labeled indication definition.

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Severe Acute Asthma in the Inpatient Setting

Kathleen B. Boyne and Kristie R. Ross

Introduction

Among the 8.6% of U.S. children with asthma, nearly half experience acute exacerbations, some of which are severe and require inpatient management (1). Severe acute asthma exacerbations, sometimes referred to as status asthmaticus, are defined as acute episodes that do not respond to initial doses of quick-relief medication and require additional care in an emergency room or hospital setting. Increasing asthma severity and the presence of exacerbations account for a substantial proportion of direct and indirect asthma-related healthcare costs (2).

Risk Factors

Although severe or life-threatening asthma exacerbations can occur even in children with mild or well-controlled asthma at baseline, several markers of poorly controlled underlying asthma are important risk factors for prolonged hospitalizations, intensive care unit stays, and death from asthma. The most consistent and strongest risk factor for future severe exacerbations is a recent previous severe exacerbation requiring oral corticosteroids, hospitalization, or intensive unit care for mechanical ventilation (3–6). Other risk factors identified across studies include increased use of quick-relief medications, comorbid chronic conditions, markers of poverty or lower socioeconomic status, and underuse of inhaled corticosteroids (3–6).

Diagnostic Tests and Monitoring Tools in Inpatient Setting

Most of the information needed to manage acute severe asthma can be obtained from a focused history and serial physical examinations, including respiratory rate and pulse oximetry (3, 4). Physical findings that should prompt concern for impending respiratory failure include single-word dyspnea; agitation, confusion, or other mental status changes; marked accessory muscle use; silent chest; and oxygen saturation less than 90%. Additional initial diagnostic testing may also be helpful in some cases (Table 2). Selected available assessment and monitoring tools

are listed in Table 3 (7–10), although a recent study found most did not show high reliability or validity, primarily due to interrater variability (11). Serial objective measurements of lung function or peak expiratory flow may be helpful if they do not delay care (12). Failure to improve with initial therapy to greater than 60% predicted FEV₁ on spirometry or personal best on peak expiratory flow measurement marks more severe exacerbations (3, 4).

Standard versus Adjunctive Therapies to Manage Severe Acute Asthma

Standard therapies with high-quality evidence for broad use in severe acute asthma in the inpatient setting include inhaled β_2 -adrenergic agonists, systemic corticosteroids, and supplemental oxygen when hypoxemia is present, as shown in Table 3 (3, 4, 13, 14). Despite advancements in understanding the underlying pathobiology of asthma and the development of new therapies for chronic asthma, there have been no recent significant advancements in the development of novel adjunctive therapies for the treatment of severe refractory acute asthma that is not responsive to bronchodilators and corticosteroids (15). Magnesium is the adjunctive therapy that is best supported by evidence (16). The addition of inhaled anticholinergics after admission is not of benefit in hospitalized children (17) when added to standard therapies. Intravenous β_2 -adrenergic agonists and methylxanthines are generally not indicated (3, 4). Although evidence is limited, in cases of impending respiratory failure not responsive to these interventions alone, initiation of noninvasive ventilation via bilevel positive airway pressure may help decrease work of breathing and need for intubation (13).

Standardized care algorithms, used to administer and wean bronchodilators, have been shown to reduce lengths of stay and costs associated with inpatient care for severe acute asthma. A comparison of care practices at six children's hospitals across a single state suggested that there are significant differences in how inpatient care algorithms are operationalized (18). There are no published data to support recommendations for specific best practices (e.g. choice of scoring system, bronchodilator delivery method, discharge education practices) for inpatient care algorithms with respect to improved length of stay, readmission rates, and costs. Most algorithms use a standardized scoring system (Table 2) and advancement criteria based on assessments performed by nursing or respiratory therapy staff, and children are generally discharged when tolerating doses of short-acting β -agonists every 4 hours.

Prevention: Minimizing Risk and Optimizing Control at Discharge

Given the consistent finding that a previous severe acute exacerbation is the strongest predictor of future severe acute exacerbations, care practices during an index hospitalization should aim to reduce the risk of relapse (3–6). Initiation or stepping up of controller medications, evaluation for comorbid conditions and allergic sensitization, reduction in environmental exposures through education and home-based interventions, provision of an asthma home management plan, establishing follow-up care with primary care providers and asthma specialists, addressing barriers to implementation of comprehensive treatment plans, and referrals to community- and school-based programs are among the practices suggested and in some cases required by regulatory agencies (3–6). Referral to multidisciplinary severe asthma clinics

Table 2. Diagnostic test and monitoring tools in the inpatient setting

	Test or Tool	Notes
Diagnostic tests	Chest X-ray (3, 4)	Not routinely recommended Obtain if: atelectasis, pneumothorax, foreign body concerns
	Arterial blood gas (3, 4)	Not routinely required Normal PaCO ₂ in context of tachypnea—sign of muscle fatigue
	Exhaled nitric oxide (4)	No role in acute management High in eosinophilic airway inflammation (>50 ppb)
Monitoring tools	Pulse oximetry (3, 4)	Serial assessments, continuous while on supplemental oxygen
	Spirometry (3, 4)	Recommended if able to obtain without delay in treatment May be more reliable than PEF FEV ₁ < 60% predicted or personal best PEF consistent with severe exacerbation Treat until plateau or patient's personal best achieved
	PEF (3)	Beneficial when poor perception of symptoms or airflow obstruction Measures can differ by up to 20% between meters—use same one PEF < 60% personal best consistent with severe exacerbation
Scoring systems	PASS (7)	Assess need for interventions in children 1–18 yr Range, 0–6 Items scored: work of breathing, wheezing, and prolongation of expiration
	PAS (8)	Items scored: respiratory rate, oxygen saturation, auscultation, retractions, and dyspnea Range, 5–15 Mild (5–7); moderate (8–11); severe (12–15)
	PRAM (9)	Assess need for admission in children aged 2–17 yr, check hourly Range, 0–12 Items scored: oxygen saturation, suprasternal retraction, scalene muscle contraction, air entry, and wheezing Mild (0–3); moderate (4–7); severe (8–12) 3-h PRAM score best predicts hospitalization
	RAD score (10)	Items scored: respiratory rate, accessory muscle use; decreased breath sounds Range, 0–3

Definition of abbreviations: PAS = Pediatric Asthma Score; PASS = Pediatric Asthma Severity Score; PRAM = Pediatric Respiratory Assessment Measure; PEF = peak expiratory flow; RAD = reactive airway disease.

can facilitate many of these interventions, although further work is needed to establish the most effective delivery methods.

Conclusions

Inpatient evaluation and management of children with severe acute asthma requires frequent, ongoing monitoring to allow for the prompt escalation of care as necessary. This is in part facilitated by scoring systems and inpatient care algorithms. Additional study is needed not only on these evaluation tools but also on adjunctive therapies and interventions available to manage these challenging patients.

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Table 3. Standard and adjunctive therapies used in severe acute asthma

	Drug	Notes
Standard therapies	Selective β_2 -agonists: INH Albuterol Salbutamol Levalbuterol	Continuous administration preferred for very severe exacerbations Monitoring for hypokalemia and tachycardia may be warranted when high doses or prolonged continuous administration required When able to wean doses, administration via MDI with spacer preferred Dose: 2.5 mg solution or 6 puffs every 20 min $\times$ 1 h, then every 1–4 h; continuous 0.5 mg/kg/h up to 10–15 mg/h
	Systemic corticosteroids: oral, IM, or IV	Administer within 1 h of presentation Oral administration is as effective as IV, less expensive, and less invasive Dose: No indication for doses above equivalent of prednisolone 1–2 mg/kg up to max of 40–60 mg
	Supplemental oxygen	Target arterial oxygen saturation of 93–95%
Adjunctive therapies	Magnesium sulfate: IV or INH	Most beneficial in severe acute asthma (increased FEV ₁ and PEF, reduced hospital admission) Mixed results with inhaled formulation Dose: IV, 40–50 mg/kg (max 2 g) over 20–60 min or INH, isotonic magnesium sulfate (150 mg) mixed with albuterol or ipratropium, 3 doses in the first hr
	Methylxanthines: IV Aminophylline Theophylline	No additional benefit if short-acting bronchodilators already in use Risk of severe side effects, not recommended
	Ipratropium bromide: INH	Benefit when added to SABA in the emergency department but no demonstrated benefit during hospital admission No significant added risk, recommended only in severe asthma Dose: 2 puffs of 80 μ g (or 250 μ g by nebulizer) every 20 min for 1 h, then space as tolerated
	Epinephrine: IM	If associated with anaphylaxis or angioedema
	β_2 -agonists: IV or IM Terbutaline	No added benefit or increased efficacy compared to inhaled therapy Consider if inhaled therapy unable to be appropriately administered Increased systemic side effects
	Corticosteroids: INH	Conflicting evidence for impact during acute exacerbation; initiating or increasing doses with mild exacerbations may provide benefit Consider stepping up therapy for 2–4 wk after exacerbation Reinforces importance of chronic controller therapy
	Ketamine/anesthetics	Mixed results; ketamine leads to bronchodilation and has been associated with decreased Pco ₂ in adults Inhalational anesthetics (isoflurane) anecdotally decrease airway resistance
	Heliox	Mixed results; in severe asthma, significant increase in PEF and decrease in hospitalization; may decrease Pco ₂ and hyperinflation May reduce work of breathing by decreasing resistance leading to more laminar flow Dose: most common helium-oxygen mixture 70:30
	Noninvasive ventilation	Has demonstrated some clinical improvement in a few studies when used in addition to standard therapies BiPAP: consider starting with IPAP 10 cm H ₂ O, EPAP 5 cm H ₂ O

Definition of abbreviations: BiPAP = bilevel positive airway pressure; EPAP = expiratory positive airway pressure; IM = intramuscular; INH = inhaled; IPAP = inspiratory positive airway pressure; IV = intravenous; MDI = metered-dose inhaler; PEF = peak expiratory flow; SABA = short-acting β -agonist.

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Approaches to Evaluation and Diagnosis of Childhood Interstitial Lung Disease

Laura Beth Mann Dosier and Timothy J. Vece

Introduction

Childhood interstitial lung disease (chILD) encompasses a large, heterogeneous group of individually rare disorders (1). All chILD disorders cause abnormal gas exchange and diffuse changes on lung imaging. However, not all chILD disorders affect the interstitium, and therefore the term diffuse lung disease is often used interchangeably with chILD. Although the individual diseases are rare, prevalence estimates range from 0.13 to 16 patients per 100,000 people, depending on the definition of the diseases (1).

Presenting Features

The etiology of chILD is variable, with developmental and genetic etiologies being more prevalent in infants and environmental toxins, infections, or sequelae of systemic disease more common in older children (2, 3). The patient's age (above or below the age of 2 years) greatly impacts etiologic and diagnostic considerations. There is considerable overlap in presenting signs and symptoms of patients with chILD. Many of the respiratory symptoms of chILD are nonspecific, which can make the diagnosis challenging. The most common presenting features include tachypnea (48–88%) and hypoxemia (52–86%). Other common symptoms include cough (43–63%), dyspnea

Table 4. Classification of pediatric interstitial lung disease in children younger than 2 years of age

Disorders more prevalent in infancy
Diffuse developmental disorders
Alveolar capillary dysplasia
Growth abnormalities reflecting deficient alveolarization
Alveolar simplification
Specific conditions of undefined etiology
Neuroendocrine cell hyperplasia of infancy
Pulmonary interstitial glycogenosis
Disorders of surfactant metabolism
Disorders not more prevalent in infancy
Disorders related to systemic disease
Collagen vascular disorders
Disorders of immunocompetent patients
Postinfectious lung disease
Disorders of immunocompromised patients
Opportunistic infections

(54–75%), exercise intolerance (57%), and failure to thrive (45%). Physical examination findings include crackles on auscultation (45%), clubbing, and pectus excavatum (2, 3).

Classification by Age

Although some of the interstitial lung diseases in adults are seen in children, there are a number of disorders seen exclusively in children. Due to these differences, a unique classification scheme was proposed for children younger than 2 years of age by the chILD research network (Table 4) and is now accepted as the standard classification scheme (2). Recently, the classification scheme was extended to children older than 2 years of age, with some changes to account for the different diseases seen in older children (Table 5) (3). The frequency of chILD diseases varied significantly with age, with neuroendocrine cell hyperplasia of infancy and pulmonary interstitial glycogenosis being more prevalent in infancy (12 vs. <1%), whereas disease associated with systemic disease and immunocompromised children

Table 5. Classification of pediatric interstitial lung disease in children older than 2 years of age

Disorders of immunocompetent patients
Disorders of infancy
Neuroendocrine cell hyperplasia of infancy
Alveolar simplification
Immunocompetent host
Postinfectious
Systemic disease
Collagen vascular disease
Unclassified
End-stage fibrosis
Disorders of immunocompromised patients
Opportunistic infections
Disorders related to treatment
Chemotherapy
Radiation therapy
Related to transplant and rejection
Graft- vs. host-disease
Post-transplant lymphoproliferative disease
Diffuse alveolar damage
Lymphoid infiltrates

were much more common in children older than 2 years of age (47 vs. 18%).

Systematic Approach

Due to the heterogeneity of disorders and the effect of age on the disorders seen, a systematic approach to diagnosis is required for chILD disorders. A detailed history, including evaluation of severity and progression of symptoms, birth history, family history, past medical history, and environmental exposures, is critically important. Special attention should be paid to a family history of surfactant disorders and death in infancy due to pulmonary disease. Basic laboratory testing including a complete blood count, serum chemistries, and blood gas are recommended. A sweat test should be performed to rule out cystic fibrosis if there is recurrent infection or bronchiectasis. If diffuse alveolar hemorrhage or systemic disease causing lung disease is suspected, testing for antineutrophil cytoplasmic antibodies, proteinase 3 antibodies, myeloperoxidase antibodies, and antinuclear antibodies is appropriate.

Chest imaging is recommended in chILD, with controlled-ventilation high-resolution chest CT scan being preferred (4, 5). In younger children, sedation or anesthesia may be required for control of ventilation for imaging. In certain clinical presentations, such as neuroendocrine hyperplasia of infancy and bronchiolitis obliterans, a CT scan may be diagnostic and can obviate the need for lung biopsy (1, 6). Finally, pulmonary function testing is often performed in chILD. Full pulmonary function testing, including spirometry, plethysmography, and diffusion capacity for carbon monoxide should be performed in older children and will commonly reveal a restrictive pattern (decreased FVC and FEV₁ with normal to elevated FEV₁/FVC ratio) with decreased diffusion capacity. Infant pulmonary function testing can be performed on children younger than 2 years of age who are stable enough for the procedure. Infant pulmonary function testing will often show a pattern similar to spirometry in older children, with the notable exception of neuroendocrine hyperplasia of infancy, where they will have an air trapping pattern (elevated functional residual capacity and residual volume).

Considerations for Genetic Testing

Genetic testing has increased in frequency and importance in chILD disorders. Individual gene sequencing for a disorder of surfactant metabolism, including surfactant protein B, surfactant protein C, ATP binding cassette protein A3 (ABCA3), and NK2 homeobox 1 (NKX2.1), should be performed before lung biopsy in suspected cases unless the patient is critically ill and a biopsy is required for treatment decisions (4, 5). Recently, the spectrum of immune dysregulation with pulmonary manifestations has been expanded with the discovery of multiple new genetic causes. Mutations in the coatamer subunit α gene (COPA) lead to familial lung disease with either pulmonary hemorrhage or interstitial lung disease (7). Signal transducer and activator of transcription 3 (STAT3) gain-of-function mutations and mutations in lipopolysaccharide-responsive, beige-like anchor protein (LRPA) both cause lymphoproliferative disease and should be considered in patients with a compatible clinical picture (8, 9). Although readily available, genetic testing can lead to identification of sequence variants of unknown clinical significance. If such a variant is found, further workup, including lung biopsy, may be needed for interpretation of the contribution of the genetic variant to clinical disease.

Considerations for Lung Biopsy

Two recent publications detail a systematic approach necessary for the proper evaluation of chILD disorders, including a recent ATS guideline for children younger than 2 years of age (Figure 2) (4). The chILD European Union group also recently published similar guidelines (5). Importantly, genetic testing and CT scans were recommended before lung biopsy in most children. However, lung biopsy is still required in some cases of chILD. Lung biopsies should be handled according to published guidelines (10) and should be reviewed by a pathologist with experience in chILD disorders.

Conclusions

The chILD disorders are heterogeneous, and evaluation and diagnosis are often complicated. By using known classification schemes, paying close attention to the age at diagnosis, and applying a systematic approach, physicians can better manage these complex patients.

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Figure 2. (A) Algorithm for hospitalized patient with a negative family history of interstitial lung disease. (B) Algorithm for hospitalized patients with a family history of interstitial lung disease. (C) Algorithm for outpatients with interstitial lung disease. Note the frequent use of computed tomography scans in the diagnosis and the importance of genetic testing, especially in children with a family history of lung disease. BAL = bronchoalveolar lavage; CHD = congenital heart disease; chILD = childhood interstitial lung disease; CF = cystic fibrosis; CVHRCT = controlled-ventilation high-resolution computed tomography; EKG = electrocardiogram; E.M. = electron microscopy; ILD = interstitial lung disease; iPFT = infant pulmonary function testing; NEHI = neuroendocrine cell hyperplasia of infancy. Adapted from Reference 18 by permission from the ATS.

Interstitial Lung Disease: Management and Treatment

Alicia M. Casey and Sebastian K. Welsh

Introduction

Due to the rarity of chILD and lack of any controlled therapeutic trials to date, treatment and management are based on the expertise and experience of pediatric pulmonologists. Treatment options in chILD require an understanding of the pathology of the specific underlying disease to avoid therapies that may be harmful or ineffective. Expert physician networks have been established in North America, Europe, and Australia to develop consensus treatment recommendations, on which this review is based (1–3).

Approach

Optimizing nutrition, mitigating other disease processes such as aspiration, and minimizing infection risk are the mainstays of chILD treatment. Nutritional support is critical for pulmonary and systemic health in chILD. Significant caloric supplementation, including use of gastrostomy tube feedings, may be required to overcome the increased metabolic demand of respiration in these children. In addition, the severity of increased work of breathing may increase the risk of aspiration. Patients should also have proper immunizations, avoid environmental pollutants, and receive appropriate treatment of respiratory infections.

Management of gas exchange abnormalities is also essential in the management of chILD (4). Gas exchange may be monitored by a variety of methods, such as overnight oximetry, polysomnogram, venous or arterial blood gases, blood chemistry with bicarbonate, and exercise saturation testing (1, 3, 5). Supplemental oxygen use should be administered to correct hypoxemia while at rest, during sleep, and with exertion. Screening for pulmonary hypertension, a significant predictor of mortality (6), should be performed with echocardiogram for any patient with chILD. If detected, the recommended oxygen saturation target is greater than 94% (6).

Steroids

Systemic steroids are often used for the antiinflammatory effects in some cases of chILD, although there is a lack of controlled studies, and the benefits versus adverse effects have not been formally studied (5). In general, the disorders with pathology consistent with active inflammation, such as surfactant protein–associated disorders, immune vasculitides, or interstitial lung disease (ILD) in the lymphoproliferative spectrum, can be steroid responsive (1, 3, 5, 6). Long-term steroids should be avoided in alveolar growth disorders due to concern for impaired lung parenchymal growth (1, 5). Patients with neuroendocrine cell hyperplasia of infancy are generally not responsive to long-term steroids and gradually improve over time with supportive therapy and oxygen supplementation (1, 3, 7).

Oral prednisolone, oral prednisone, and intravenous methylprednisolone are the most common glucocorticoid agents used in chILD. Prednisolone or prednisone is typically administered orally at 1 to 2 mg/kg/d. As there is a lack of evidence, the duration of treatment is determined by response or lack thereof.

Intravenous methylprednisolone can be used at a dose of 10 to 30 mg/kg/d for 3 consecutive days monthly for either more severe disease, exacerbations, or to mitigate adverse effects of chronic steroid therapy in steroid-responsive patients. A lower dose of oral steroids is used between pulses, if symptoms are recurring or worsening between pulses (1, 3, 5, 6). Patients undergoing chronic steroid therapy should be monitored for adverse effects, such as hypertension, hyperglycemia, impaired growth, low bone density, ophthalmologic complications, and adrenal suppression. Steroid-sparing agents, including disease-modifying antirheumatic drugs, calcineurin inhibitors, antiproliferative agents, mechanistic target of rapamycin inhibitors, biologic agents, and immunomodulatory dosing of intravenous immunoglobulin, should be sought whenever possible to avoid steroid toxicities.

Hydroxychloroquine

Hydroxychloroquine or chloroquine has been used in a number of different ILD diagnoses for immunologic effects, although the exact mechanisms of action are unknown. The earliest reports of its efficacy were for “diffuse interstitial pneumonitis,” a diagnosis based on pathology before the discovery of the underlying gene defects noted. Hydroxychloroquine can be used as monotherapy or as adjunctive therapy with steroids or other immunologic medications. Hydroxychloroquine is often used in the treatment of surfactant protein–associated disorders, including surfactant protein C dysfunction and ABCA3 deficiency, with positive effect in many cases but no clear effect in others (1, 8, 9). In addition, positive outcomes are reported in treating immune dysfunction–associated disorders (5). Hydroxychloroquine is administered orally at a dose of 5 to 10 mg/kg/d, with clinical improvement typically seen in 1 to 3 months from starting therapy (1, 3, 5, 8, 10). Gastrointestinal side effects are most common. Ophthalmic examination should be performed before starting hydroxychloroquine and at regular intervals during treatment, as hydroxychloroquine is associated with ocular toxicity (9).

Other Treatments

For treatment of pulmonary alveolar proteinosis, the only established therapy available is repeated whole-lung lavage (3). Inhaled granulocyte macrophage-colony stimulating factor showed benefit in small, uncontrolled studies in autoimmune pulmonary alveolar proteinosis (11–13). Azithromycin is often used in chILD and has demonstrated some benefit in bronchiolitis obliterans, although randomized controlled trials in pediatric postinfectious bronchiolitis obliterans are lacking (5). Azathioprine, methotrexate, etanercept, cyclosporine, rituximab, intravenous immunoglobulin, and other immunologic therapies have been used with varying success (1–5, 7, 14, 15, 16). These additional therapies should be considered with the assistance of a rheumatologist or immunologist and targeted toward the underlying defect. Referral to a center with expertise in chILD can assist in using additional therapies.

Lung Transplantation

Lung transplantation in patients with severe chILD has similar outcomes to cystic fibrosis and pulmonary vascular disease (1, 3, 5). Patients with pulmonary hypertension, growth failure, and severe fibrosis have the highest risk for mortality. Every effort

should be made to avoid these complications by intervening as early as possible with effective supportive care, nutritional support, and antiinflammatory therapy if indicated (5). The prognosis for chILD is highly variable, and thus if a patient is stable or improving, chronic ventilation (noninvasive or through a tracheostomy tube) can also be considered as an alternative to transplantation (17). In general, a patient with a severe course consistent with chILD should be referred to a lung transplantation center with experience in managing chILD.

Conclusions

The management of severe chILD focuses on supportive care, with variable responses to limited treatment options, including corticosteroids and hydroxychloroquine. Lung transplantation remains an option for patients with refractory disease.

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Pathophysiology and Management in Bronchopulmonary Dysplasia

J. Wells Logan and Edward G. Shepherd

Introduction

Epidemiologic evidence suggests that bronchopulmonary dysplasia (BPD) is increasing in frequency among infants born at less than 32 weeks gestational age (1). Higher survival rates correlate with advances in care, but survival benefit is accompanied by increases in pulmonary and neurocognitive morbidity. Increasing survival rates explain, at least in part, why respiratory morbidity is increasing in prevalence among infants born preterm. The definition of BPD is also evolving, primarily due to the need for well-defined respiratory outcomes in research studies. The current consensus definition (i.e., oxygen need at 28 d and/or 36 wk gestational age) was introduced to provide a uniform framework for evaluating clinical research interventions. This definition, however, provides very little insight into the nature and severity of the underlying pulmonary abnormality.

BPD Phenotype

The BPD phenotype correlates better with disease severity than with the need for oxygen at 36 weeks and depends largely on the developmental state of the airway at birth (2). Infants born in the first (embryonic) and second (pseudoglandular) stages of lung development have insufficient airway development to survive extrauterine life. Infants born during the late third (canalicular) or early fourth (saccular) stages of lung development may survive but frequently have significant pulmonary and neurocognitive morbidity. The pathophysiology correlates with arrested or interrupted development of alveolar saccules, conducting airways, and interstitium and with dysregulated surfactant production and pulmonary vascular development (2). Before the availability of surfactant and antenatal steroids, the lungs of infants with BPD were characterized by a fibroproliferative response, small airway (epithelial metaplasia) injury, and alveolar growth abnormalities. Despite the benefits of surfactant and antenatal steroids, infants born in recent epochs of care (i.e., at earlier gestations) have fewer alveoli, larger and more simplified airways, and dysmorphic pulmonary vasculature (3).

Impact of Disease Progression on Pulmonary Outcomes

Although the clinical phenotype derives largely from the timing of injury, disease progression derives from antenatal, perinatal, and postnatal exposures that modify lung function and development (2). A variety of genetic, endogenous, and exogenous (antenatal steroids) factors influence the respiratory course before the infant is even born (2). The quality of neonatal resuscitation, the presence or absence of infection, and the duration of exposure to oxygen and positive pressure ventilation each potentially impact outcome (2).

Exposure to oxygen and mechanical ventilation, clinical correlates of BPD, are significantly associated with inflammation (4) and, subsequently, with adverse pulmonary (5) and neurocognitive (6) outcomes. The net effect of these exposures, positive or negative, determines the long-term pulmonary and neurocognitive course.

Approach to Optimize Pulmonary Outcomes

There is no single management strategy for the wide spectrum of clinical presentations. Underlying the clinical approach is the knowledge that once BPD is established, preventative strategies are no longer appropriate. Infants with a less severe phenotype have mild diffusion defects, requiring only nasal cannula oxygen or continuous positive airway pressure. Using the current definition, these infants have either “moderate” or “severe” BPD, respectively. Despite the notion that the current definition conveys, with optimal care these infants can have favorable long-term outcomes. Those requiring mechanical ventilation at 36 weeks gestational age (or beyond), however, have a more severe phenotype and are at greater risk of adverse pulmonary and neurocognitive outcomes. In extreme cases, tracheostomy tube placement may be required.

Regardless of the BPD phenotype, the support apparatus should match the disease physiology. An individualized approach is needed—one that optimizes positive influences and minimizes negative ones. For the severe phenotype especially, provision of adequate $\dot{V}/\dot{Q}$ matching and oxygen saturations are essential for stabilizing respiratory status, minimizing pulmonary vascular dysregulation, and achieving metabolic and developmental gains (7). Comfortable respirations and positive developmental signs (e.g., a quiet alert state), if accompanied by lean tissue and linear growth, provide some evidence for a net positive balance.

Perhaps the most promising strategy for achieving an optimal respiratory outcome is to avoid mechanical ventilation altogether (8). By extension, the best possible neurocognitive outcome is achieved by optimizing respiratory and other supportive measures (e.g., nutrition) and by minimizing potentially adverse exposures (7). Thus far, the only pharmacologic therapies found to reduce the incidence of BPD are caffeine citrate, vitamin A, clarithromycin, and corticosteroids (9). Caffeine is used widely and is associated with improvements in both respiratory and neurocognitive outcomes (10). Vitamin A has been used by some, with variable results. Systemic corticosteroids are associated with improvements in pulmonary function but are also associated with neurocognitive consequences. Macrolide antibiotics and inhaled corticosteroids still hold some promise, but, generally speaking, more research is needed before many of these agents can be used routinely (9).

Conclusions

BPD is increasing in frequency among infants born very preterm. The widely variable clinical phenotypes derive

largely from the timing of injury and inform the management strategy.

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BPD and Outpatient Management

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Introduction

BPD is a chronic lung disease that most often develops in premature infants. It is defined by the requirement for supplemental oxygen and/or respiratory support at a postmenstrual age of 36 weeks in infants less than 32 weeks gestation and at 29 to 55 days after birth in infants 32 weeks gestation or greater.

Phenotypes

Two dominant forms of BPD are described: “old” or “classic” BPD, originally reported in mildly preterm newborns with respiratory distress syndrome exposed to aggressive mechanical ventilation and high concentrations of supplemental oxygen, and “new” BPD, characterized by arrested development of alveoli and microvasculature in preterm and extremely preterm infants (1). Despite advances in neonatal care, both forms of BPD remain a

concern. The underlying pathophysiology of these phenotypes provides a rationale for a number of therapies that are routinely used in infants with BPD after nursery discharge. There is, however, limited evidence supporting their use.

Bronchodilators

Recurrent wheeze and cough are common symptoms of infants and children who survive prematurity with BPD. There is an increased risk of abnormal baseline spirometry and exercise-induced bronchoconstriction in school-aged patients with BPD. In classic BPD, small airway obstruction results from hypertrophied airway smooth muscle and neutrophilic inflammation. The alveolar simplification seen in “new” BPD can lead to a reduced airway caliber and a propensity toward airway narrowing with smooth muscle contraction. A substantial proportion of patients with BPD will have a significant response to bronchodilator treatment (2, 3).

Inhaled Corticosteroids

Episodic acute illness characterized by cough and wheezing occurs in the majority of infants and toddlers with BPD. These episodes are believed to result from infection or aspiration, which cause inflammation and bronchospasm. The bronchospasm is notably not associated with eosinophilic inflammation as it is in atopic asthma. Despite this difference in the etiology of inflammation, corticosteroids are sometimes used to treat or prevent pulmonary exacerbations. Inhaled corticosteroid use is theorized to reduce inflammation, enhance surfactant production, and decrease fibrosis. A study of 18 formerly preterm infants, half of whom had BPD, has shown a decrease in cough and wheeze, need for bronchodilators, and air trapping as measured by helium gas dilution over a 6-week trial period (4). However, there are no studies replicating these findings and few studies evaluating corticosteroid treatment in the infant with established BPD. These treatments are also associated with potential side effects, and thus the risk-to-benefit ratio is unknown.

Diuretics

Infants with BPD are believed to have a predisposition to the development of interstitial pulmonary edema from dysmorphic microvasculature, increased pulmonary vasculature pressures, dilated lymph vessels, increased capillary permeability from lung injury, heart failure, and generalized fluid overload. This can result in increased airway resistance and reduced pulmonary compliance. Furosemide, a loop diuretic, has been shown to help reduce airway resistance and increase dynamic pulmonary compliance in spontaneously breathing patients with BPD acutely and subacutely (5, 6). In addition, distal diuretics, such as thiazides or potassium-sparing diuretics, have also been shown in a large meta-analysis to improve lung function acutely and over a 4-week treatment period (7). However, diuretics are associated with adverse effects, including metabolic alkalosis, electrolyte abnormalities, hypercalciuria, and nephrocalcinosis. Whether long-term use of these drugs results in improved clinical outcomes has yet to be determined. Diuretic therapy may be an attractive option, at least in the short term, for those infants requiring high levels of supplemental oxygen, those with interstitial edema, and those with associated cardiac disease.

Supplemental Oxygen

Approximately one-third of patients with BPD will be discharged from the hospital dependent on supplemental oxygen. Achieving normoxia, through the appropriate use of supplemental oxygen, helps infants with BPD grow better. Most patients do not require oxygen supplementation after a year or two of life (8). However, there is generally no consensus on how to approach the withdrawal of supplemental oxygen (9); infants with BPD are particularly prone to hypoxemia while sleeping as well as before, during, and after feedings (10). Some authors advocate performing polysomnography to assess for sleep-associated hypoxemia (11, 12). The lower limit for acceptable oxyhemoglobin saturation targets and the safest and most expeditious way to wean supplemental oxygen support remain areas of clinical controversy (13).

Conclusions

Patients with BPD face a number of challenges in the arduous period after initial hospital discharge. There are few large randomized controlled trials focusing on pertinent clinical outcomes for this patient population. However, consideration of the underlying pathophysiology can direct a rational approach to pharmacologic treatment.

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Pediatric Pulmonary Hypertension

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Introduction

Pulmonary hypertension (PH) is a high morbidity and mortality constellation of conditions in both adults and children. In many cases, the underlying etiologies, outcomes, and treatment strategies in the pediatric population are distinct from those in adults. One reason for this distinction is the intimate link between the pulmonary vasculature and lung growth and development in the pediatric population. Several studies have shown that impaired angiogenesis in the developing lung leads to decreased alveolarization (1). Alternatively, aberrations in lung development can cause abnormal pulmonary vascular development. Stressors, such as hypoxia, inflammation, infection, and altered hemodynamics can lead to vascular damage and remodeling and eventually the development of PH.

Table 6. Nice World Health Symposium classification of pulmonary hypertension

1 Pulmonary arterial hypertension
1.1 Idiopathic PAH
1.2 Heritable PAH
1.2.1 BMPR2
1.2.2 ALK1, ENG, Smad 9, CAV1, KCNK3
1.2.3 Unknown
1.3 Drug and toxin induced
1.4 Associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1' Pulmonary venoocclusive disease and/or pulmonary capillary hemangiomatosis
1'' Persistent PH of the newborn
2 PH due to left heart disease
2.1 LV systolic or diastolic dysfunction
2.2 Valvular disease
2.3 Congenital left heart inflow, outflow tract obstruction, congenital cardiomyopathies
3 PH due to lung disease and/or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other mixed restrictive and obstructive lung diseases
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases
4 Chronic thromboembolic PH
5 PH with unclear multifactorial mechanisms
5.1 Hematologic disorders
5.2 Systemic disorders
5.3 Metabolic disorders
5.4 Others: tumor obstruction, fibrosing mediastinitis, chronic renal failure, segmental PH

Definition of abbreviations: ALK1 = activin receptor-like kinase-1; BMPR2 = bone morphogenic protein receptor type II; CAV1 = caveolin-1; ENG = endoglin; KCNK3 = potassium two pore domain channel subfamily K member 3; LV = left ventricular; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension.

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Classification Schemes

The classification of pediatric PH used most frequently, the Nice World Health Symposium Classification Scheme (Table 6), focuses on five major groups of disorders and incorporates pediatric-focused conditions (2). In particular, pediatric lung disease, BPD, congenital diaphragmatic hernia, and other developmental lung diseases have been highlighted. In addition, left outflow tract obstruction has been added, including disorders such as pulmonary vein stenosis, coarctation of the aorta, and valvular stenosis. Although the Nice scheme helps guide workup, the Panama classification scheme of pediatric PH is a useful tool to categorize pediatric PH, because it incorporates pediatric-relevant concepts such as impaired lung growth and development, congenital disorders, and prematurity-associated lung conditions (Table 7) (3).

An important concept in PH care is the functional capacity of a child, which influences prognosis and treatment response. The Panama Functional Classification system, the first such system for children with PH, was published in 2011 (4). It follows the same pattern of adult classification schemes for cardiovascular impairment (World Health Organization and New York Heart Association systems), with four classes of disease severity; however, the Panama system is divided into five separate age groups to take into account age-appropriate developmental milestones and the patient's ability to articulate symptoms. Although further studies are needed, retrospective evaluation of this system to functionally categorize children does appear to predict the risk of clinical demise over time (5).

Functional Measures

Consensus guidelines by the American Heart Association and ATS for the care of children with PH were published in 2015 (1). This

Table 7. Panama classification of pediatric pulmonary hypertension

1. Prenatal or developmental Example: congenital diaphragmatic hernia
2. Perinatal pulmonary vascular maladaptation Example: persistent pulmonary hypertension of the newborn
3. Bronchopulmonary dysplasia and prematurity-associated lung disease
4. Congenital heart disease
5. Isolated pediatric pulmonary hypertensive vascular disease Examples: idiopathic PAH, familial BMPR2-PAH, PVOD
6. Congenital abnormalities or malformations with multifactorial disease entities Example: trisomy 21
7. Pediatric lung disease Examples: interstitial lung disease, sleep disordered breathing, cystic fibrosis
8. Thromboembolic disease
9. Hypobaric hypoxic exposure
10. Associated with other system disorders Examples: hemolytic anemia, metabolic disorders, portal hypertension

Definition of abbreviations: BMPR2 = bone morphogenic protein receptor type II; PAH = pulmonary arterial hypertension; PVOD = pulmonary venoocclusive disease.

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comprehensive document includes guidance on making the diagnosis of PH and treatment strategies. When PH is suspected, echocardiography is a useful modality to assess cardiac structure and function and estimate right ventricular pressure (1, 6). Echocardiography may also be used as a screening tool with high-risk populations, such as those with BPD. Additional components of the evaluation for PH include chest imaging, pulmonary function testing (when able), and certain laboratory assessments, including brain natriuretic peptide or N-terminal-pro-brain natriuretic peptide (6). Cardiac catheterization with angiogram and acute vasodilator testing is recommended before initiating long-term pulmonary arterial hypertension-targeted therapy in all patients, unless the child is critically ill requiring urgent medication initiation or is intolerant of the procedure (7). Follow-up includes repeat echocardiogram and pulmonary function testing every 3 to 6 months, or as clinically indicated. Cardiac catheterization should be repeated 3 to 12 months after change in therapy and then every 1 to 2 years, although choice on timing will be specific to clinical course and the individual's risk of undergoing the procedure (1).

Treatment

The treatment of PH in children includes pharmacotherapeutics and supportive care of comorbid conditions. The use of supplemental oxygen to maintain normoxia is a mainstay of treatment. Inhaled nitric oxide is a direct pulmonary vasodilator that is used in the acute setting and in acute vasodilatory testing during cardiac catheterization. The acute use of inhaled nitric oxide is the only medication approved by the U.S. Food and Drug Administration for children with PH. Long-term medication options arise from three major classes of pulmonary vasodilators: prostacyclin and prostacyclin derivatives, endothelin receptor antagonists, and phosphodiesterase type 5 inhibitors. Delivery methods include intravenous, subcutaneous, inhaled, and oral regimens. Depending on disease severity, patients may require medications in all three classes, with multiple modes of delivery.

Table 8. Indicators suggestive of high risk of clinical decline in pediatric pulmonary hypertension

Evidence of right ventricular failure
Rapid progression of symptoms
Syncopal events
Poor growth parameters
WHO/NYHA functional class III or IV
Significantly elevated or increasing BNP or NT-proBNP level
6MWT < 300 m
CPET peak $\dot{V}O_2 < 15$ ml/kg/min
Cardiac catheterization data showing hemodynamic decline
Systemic cardiac index < 2.5 L/min/m ²
Mean PAP/mean SAP > 0.75
Right atrial pressure > 10 mm Hg
Pulmonary vascular resistance index > 20 WU · m ²

Definition of abbreviations: 6MWT = 6 minute-walk-test distance; BNP = brain natriuretic peptide; CPET = cardiopulmonary exercise testing; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PAP = pulmonary arterial pressure; SAP = systemic arterial pressure; WHO = World Health Organization; WU = Wood units.

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Medication approaches are based largely on clinical experience and the extension of adult-focused clinical trials. Most treatment algorithms for pediatric PH suggest consideration of the risk of clinical demise in determining the best options for treatment. Those at higher risk demand more aggressive treatment with PH-specific vasodilator therapies. Indices suggestive of a high risk of clinical decline include a number of factors, as listed in Table 8 (8). In addition, screening for and treatment of comorbid conditions, such as dysphagia and obstructive sleep apnea, is crucial. Supportive family care approaches, including child life and palliative care specialists, can be useful, depending on the family and severity of disease. Overall, children with PH require a thoughtful, comprehensive, family-centered approach.

Conclusions

PH encompasses a heterogeneous group of etiologies in children that result in a wide variation in outcome. Echocardiographic imaging and cardiac catheterization data are critical in management, and treatment is focused on PH-specific medications in combination with management of comorbid conditions.

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Pulmonary Manifestations of Pediatric Rheumatologic Diseases

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Introduction

Rheumatologic diseases comprise a diverse group of disorders affecting virtually any organ in the body. The respiratory system can be the primary organ involved with acute presentations, such as the antineutrophilic cytoplasmic antibodies (ANCA)-associated vasculitides, or as an insidious source of morbidity in systemic connective tissue diseases. Early recognition of pulmonary and extrapulmonary manifestations is crucial for a timely diagnosis to prevent subsequent morbidity and mortality.

ANCA-associated Vasculitides

ANCA-associated vasculitides include granulomatosis with polyangiitis (GPA, formerly Wegener's), microscopic polyangiitis, and eosinophilic granulomatosis with polyangiitis (formerly Churg-Strauss) and characteristically cause necrotizing granulomatous inflammation of small and medium blood vessels, which preferentially affect the pulmonary and renal systems.

GPA is the most common of the ANCA-associated vasculitides, with an estimated incidence of 0.5 per 100,000 per year, occurring predominantly in the second decade of life (1). Patients frequently present with pulmonary symptoms (~70%) including chronic cough, dyspnea, hemoptysis from alveolar hemorrhage, and hypoxemia. GPA tends to involve the upper airway, and patients can present with chronic sinusitis, epistaxis, mucosal ulcerations, laryngotracheobronchial stenosis, and the pathognomonic saddle-nose deformity (Figure 3A) (2). Radiologic findings include lung nodules, fixed infiltrates, cavitations, and the reverse halo sign, a central ground-glass opacity surrounded by denser consolidation in a ring shape, often seen in alveolar hemorrhage (3). Nodules with central cavitations, referred to as "pulmonary cheerios," can also be seen in GPA (Figure 3B). Diagnostic criteria for GPA include finding two or more features: nasal or oral inflammation, abnormal

chest imaging, urinary sediments, and supporting biopsy. The presence of proteinase 3 (PR)-ANCA (cytoplasmic pattern) is more common in GPA (2). Microscopic angiitis less often involves the lungs. Compared with GPA, patients with microscopic angiitis are more likely to have a positive myeloperoxidase-ANCA (perinuclear pattern) (2). Eosinophilic GPA usually has a prodromal phase of asthma, allergic rhinitis, and nasal polyposis. It is followed by eosinophilic pulmonary infiltrates and then vasculitis (4).

Treatment of ANCA-associated vasculitides is extrapolated from studies in adults and involves the use of glucocorticoids, cyclophosphamide, or rituximab for remission induction. This is followed by maintenance immunosuppression. Plasma exchange is reserved for life-threatening pulmonary hemorrhage or rapidly progressive renal disease (5).

Antiglomerular Basement Membrane Disease

Antiglomerular basement membrane disease (Goodpasture syndrome) is a rare autoimmune disease that involves the lungs and kidneys. Patients often present with acute renal failure from rapidly progressive glomerulonephritis with or without pulmonary hemorrhage. It is distinguished from ANCA-associated vasculitides by serum antiglomerular basement membrane antibodies and histopathologic findings of crescentic glomerulonephritis with linear deposits of IgG and C3 along the glomerular basement membrane detected using immunofluorescence (6).

Pulmonary Complications of Systemic Connective Tissue Disease

Pulmonary manifestations can often complicate systemic connective tissue diseases. Scleroderma is an autoimmune disease that results in hardening of the skin. There are two main forms: a localized form and a systemic form. Pulmonary complications are more common in systemic scleroderma (30–70%) and include interstitial lung disease, pulmonary fibrosis, or pulmonary arterial hypertension (7). Patients also frequently have impaired gastrointestinal motility and recurrent aspiration.

Figure 3. (A) Profile view showing saddle-nose deformity in patient with limited granulomatosis and polyangiitis. (B) High-resolution computed tomography scan of the chest in the same patient on axial view showing 2.3 × 2 cm pulmonary nodule with central cavitation, so-called "pulmonary cheerio" (arrow).

Juvenile dermatomyositis is an inflammatory disease of the muscle, skin, and blood vessels that affects three per million children each year. Juvenile dermatomyositis is characterized by unique rashes and myositis, the latter potentially causing restrictive lung disease from respiratory muscle weakness. Interstitial lung disease can complicate juvenile dermatomyositis. The presence of anti-Jo-1 and melanoma differentiation-associated protein 5 autoantibodies are associated with a higher incidence and mortality from interstitial lung disease (8).

Mixed connective tissue disease is a rare connective tissue disorder with overlapping symptoms of connective tissue disorders. Patients can have variable pulmonary involvement similar to other connective tissue disorders and often have high titers of anti-U1 small nuclear riboprotein antibodies.

Systemic lupus erythematosus is renowned for its myriad of manifestations. The majority of pulmonary symptoms are present during initial presentations or acute flares, most common being pleurisy or pleural effusion. However, more severe involvement with pneumonitis or alveolar hemorrhage has been reported. Thromboembolic events, including pulmonary embolism, occur with greater frequency in the presence of antiphospholipid antibodies.

Extrapulmonary manifestations, if recognized, can aid in the early diagnosis of these diseases. Common cutaneous features in systemic connective tissue diseases include the malar rash in systemic lupus erythematosus, and heliotrope, shawl-sign, and Gottron rashes in juvenile dermatomyositis. Patients with systemic scleroderma have tense nonpitting edema of the hands and face that progress to shiny, sclerotic skin. Both systemic scleroderma and juvenile dermatomyositis can display abnormal nailbeds, with erythema and dilated capillaries. Urine studies can reveal hematuria or proteinuria seen in vasculitides or systemic lupus erythematosus.

Complications of Treatment

Agents used to treat rheumatologic diseases can have untoward consequences. The use of tumor necrosis factor- α inhibitors is associated with an increased incidence of opportunistic infections from tuberculosis and fungi. However, overall rates of serious infections remain low (9). Interstitial pneumonitis has also been reported as a complication of methotrexate

in adults; this complication is rarely reported in children, however (10).

Conclusions

Although rare, the pulmonary manifestations of rheumatologic disease are a cause of significant morbidity and mortality and children. Early diagnosis is essential in the management of these conditions. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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