ATS Core Curriculum 2020

Pediatric Pulmonary Medicine

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ABSTRACT

The American Thoracic Society Core Curriculum updates clinicians annually in adult and pediatric pulmonary disease, medical critical care, and sleep medicine, in a 3- to 4-year recurring cycle of topics. These topics will be presented at the 2020 International Conference. Below is the pediatric pulmonary medicine core, including pediatric hypoxemic respiratory failure; modalities in noninvasive management of chronic respiratory failure in childhood; surgical and nonsurgical management of congenital lung malformations; an update on smoke inhalation lung injury; an update on vaporizers, e-cigarettes, and other electronic delivery systems; pulmonary complications of sarcoidosis; pulmonary complications of congenital heart disease; and updates on the management of congenital diaphragmatic hernia.

Keywords:
review; e-cigarettes; wildfires; sarcoidosis; pediatric

MODALITIES IN NONINVASIVE MANAGEMENT OF CHRONIC RESPIRATORY FAILURE IN CHILDHOOD

Stephen M. M. Hawkins and Christopher D. Baker

Chronic respiratory failure (CRF) is diagnosed when the need for respiratory support exceeds that expected for an acute illness or is due to a chronic condition. Children of all ages suffer from CRF because of a wide variety of acquired or congenital conditions, including airway abnormalities (upper airway obstruction and malacia), parenchymal lung disease, and neuromuscular, musculoskeletal, and sleep-related disorders. CRF may occur after an acute

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respiratory insult in a child with poor respiratory reserve because of an underlying condition. Sleep-related respiratory failure often precedes daytime respiratory failure and can be more problematic in children given their increased sleep needs and propensity for daytime napping (1, 2).

Long-Term Mechanical Ventilation

Long-term mechanical ventilation may be indicated for the treatment of CRF. The need for ventilation may signal progression from respiratory insufficiency to failure. In this context, "ventilation" refers to respiratory support devices or treatments that augment or replace the respiratory system's ability to perform oxygenation and ventilation. Ventilation can be provided invasively via tracheostomy or noninvasively via mask interface. The decision to pursue long-term invasive or noninvasive ventilation (NIV) is challenging and requires consideration of medical, social, and ethical factors as well as the services available in a given community (3).

Invasive Mechanical Ventilation

Invasive ventilation is considered for children when interruption of ventilation would be life threatening or when support is needed for the majority of waking hours. Common conditions that warrant consideration for tracheostomy include anatomic or functional upper airway obstruction, diaphragm paralysis, progressive neuromuscular disease, and severe chronic lung disease (2).

Noninvasive Mechanical Ventilation

A much larger number of children with CRF can tolerate periods of time without positive pressure support and are candidates for NIV. During these short periods, NIV and other noninvasive modalities may be completely removed, which can dramatically improve quality of life when done safely. NIV can be delivered via a nasal mask, traditional oronasal face mask, newer total face masks, or nasal pillows, which seal to the nares rather than covering the entire nose. High-flow nasal cannula (HFNC) is increasingly used as an NIV alternative. However, there is little evidence to support its use in children in the outpatient setting (4). HFNC provides heated, humidified room air with or without supplemental oxygen at flow rates that are typically >5 L/min and occasionally as high as 50–60 L/min. NIV neurally adjusted ventilatory assist is a promising ventilation strategy that obviates patient–ventilator dyssynchrony but is currently only feasible in the intensive care unit setting (5). Other potential adjuncts to NIV include diaphragmatic pacing, hypoglossal nerve stimulation, bariatric surgery, and respiratory muscle training.

In-Home Monitoring

Advancements in data monitoring can aid clinicians in optimizing NIV in the home setting. Device data reports provide confirmation that ventilator settings are appropriate, use is as prescribed, and the child's breathing is optimally supported by the current ventilation strategy (6). Cloud-based monitoring, remote interrogation, and other advances in in-home telemedicine will further improve support for children who require NIV (7).

Barriers to Success

Adherence to NIV is poor overall (8). Barriers to consistent use are related to equipment (poor-fitting interfaces, suboptimal ventilator modes or

insufficient settings, and excessive air leak), childhood behaviors (resistance to use and tactile defensiveness), inadequate parental support, and other social/financial factors. Clinicians who provide NIV benefit from pediatric-specific equipment (properly sized mask interfaces, cannulas, and devices). Multidisciplinary teams provide emotional, social, and psychological support to patients and caregivers in addition to addressing each child's unique needs (9).

Conclusions

NIV and other novel noninvasive modalities can be implemented to successfully treat CRF in the outpatient setting by multidisciplinary teams who tailor care to each child's specific medical condition and the family's goals of care. Further study is needed to determine when NIV should be used to treat children with CRF rather than approaches that are either more invasive (tracheostomy) or less invasive (oxygen therapy).

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SURGICAL AND NONSURGICAL MANAGEMENT OF CONGENITAL LUNG MALFORMATIONS

Sourav K. Bose and William H. Peranteau

Congenital pulmonary airway malformations (CPAMs) are the most common congenital lung lesion, with a prevalence of approximately 1 in 11,000 births (1). CPAMs consist of a spectrum of developmental cystic and noncystic lung malformations often associated with some degree of bronchial obstruction before birth (2). Most CPAMs can be classified into

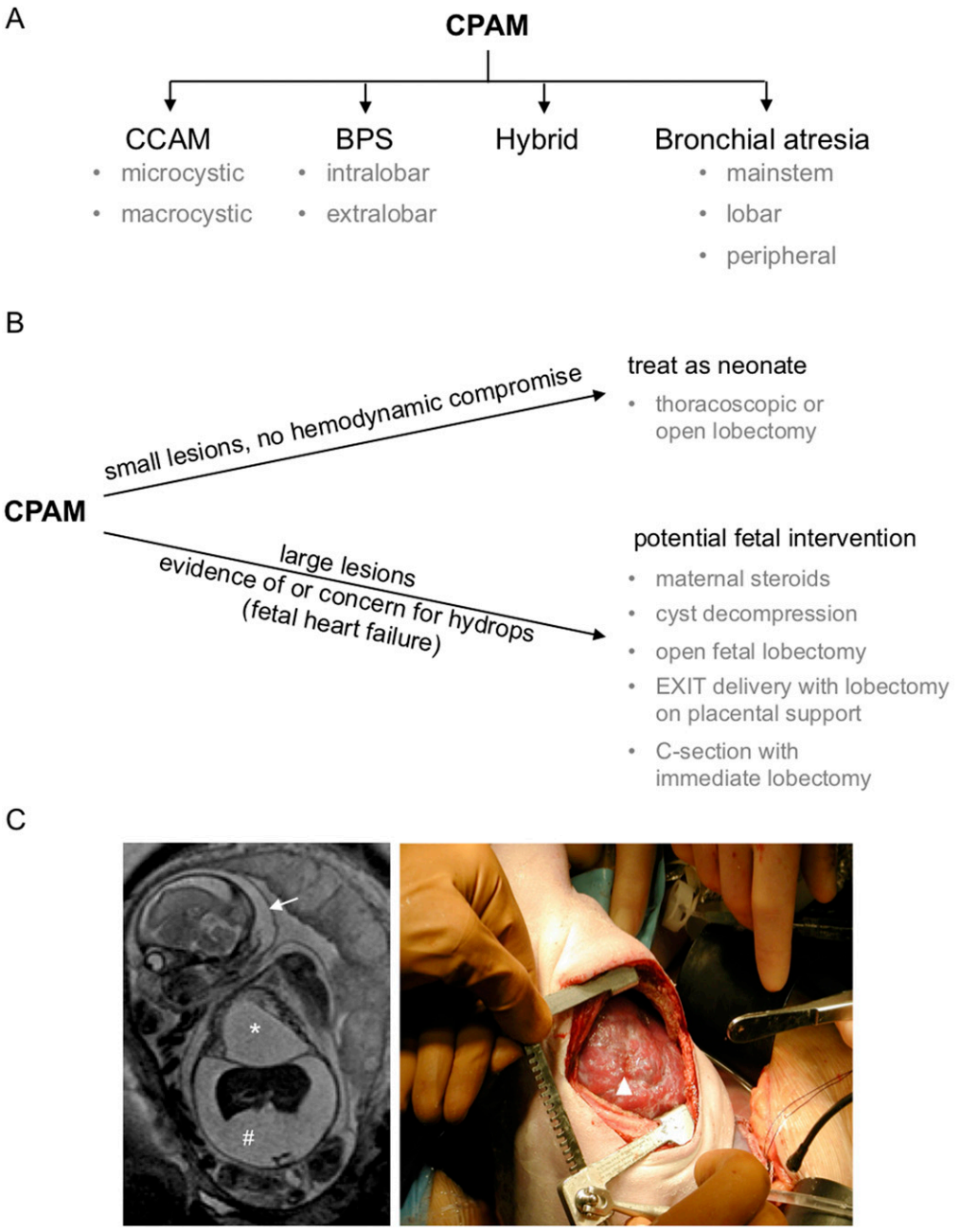

Figure 1. Congenital pulmonary airway malformation (CPAM) lesions and prenatal and postnatal management. (*A*) CPAMs consist of a spectrum of congenital lung lesions that can be diagnosed *in utero* and followed on prenatal ultrasound. (*B*) Most CPAMs are small, do not cause respiratory symptoms at birth, and can be resected via a lobectomy electively at a couple months of age. Rarely, large CPAMs can cause hemodynamic compromise before birth and are candidates for prenatal interventions, without which a high rate of fetal loss exists. (*C*, left) A 24-week fetus with large macrocystic congenital pulmonary adenomatoid malformation (*) resulting in fetal hydrops as indicated by ascites (#) and skin/scalp edema (white arrow). (*C*, right) EXIT procedure during which a large CPAM (white triangle) is resected at the time of birth via a thoracotomy while the infant is maintained on placental support. BPS = bronchopulmonary sequestrations; CCAM = congenital cystic adenomatoid malformation; EXIT = *ex utero* intrapartum treatment.

microcystic or macrocystic congenital pulmonary adenomatoid malformations, bronchopulmonary sequestrations (BPS; characterized by an abnormal systemic feeding vessel and either pulmonary [intralobar] or systemic [extralobar] venous drainage), hybrid lesions (characteristics of CPAMs and BPS), or

bronchial atresias (mainstem, lobar, and peripheral bronchial atresias) (Figure 1A).

Advances in prenatal imaging, including ultrafast fetal magnetic resonance imaging and serial prenatal ultrasounds, allow for the diagnosis of most CPAMs before birth; thus, the natural history of these lesions is known. Most lesions grow in absolute and relative (as measured by the CPAM volume ratio) size until 26–28 weeks of gestation (3). Although some lesions are not detectable at the end of gestation, lesions do not completely regress, and postnatal follow-up is required for all patients. Most affected infants are asymptomatic at birth, do not require any prenatal intervention, and can been seen as outpatients at 1–2 months of age, at which time a low-dose irradiation chest computed tomographic (CT) scan with contrast is performed.

Surgery is generally recommended for all infants with CPAMs but may not be required for those with small extralobar BPS, which tend to regress over time (Figure 1B). Although surgical resection for symptomatic lesions (i.e., those that are infected or causing respiratory compromise) is well accepted, whether surgery is indicated for asymptomatic lesions is a point of debate (4, 5). The indications for surgery (for both symptomatic and asymptomatic lesions) include the increased risk of infection/pneumonia and the small risk of cancer (2) combined with the low risk of surgical complications (5). In addition, resection in infancy allows for compensatory growth of the unresected normal lobe(s) (4). Surgical technique has traditionally involved a thoracotomy with resection of the affected lobe; however, in high-volume centers, thoracoscopic resection has also been demonstrated to be safe (6). Large lesions (CPAM volume ratio > 1.6) can cause prenatal hemodynamic compromise, leading to fetal hydrops (heart failure) (Figure 1C) and/or respiratory failure at birth. In these cases, prenatal and postnatal care should occur at dedicated fetal treatment centers. These patients are potential candidates for fetal interventions, including maternal betamethasome for microcystic lesions and cyst decompression for macrocystic lesions (7, 8). On the basis of their gestational age, patients who fail to respond to betamethasone or cyst decompression may be candidates for open fetal surgery to resect the lung lesion before birth or an *ex utero* intrapartum treatment delivery, during which the lesion is resected at birth while the infant is maintained on placental support (Figures 1B and 1C) (9). The long-term outcome of infants with congenital lung malformations is very good, even for those with large lesions causing symptoms at birth (4, 10).

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INVASIVE AND NONINVASIVE MANAGEMENT OF PEDIATRIC HYPOXEMIC RESPIRATORY FAILURE

Garrett Keim and Nadir Yehya

Definitions

The 2015 Pediatric Acute Lung Injury Consensus Conference codified definitions and management principles for pediatric acute respiratory distress syndrome (PARDS) (1). Key differences from the Berlin ARDS definition include *1*) unilateral *or* bilateral infiltrates on chest imaging, *2*) inclusion of NIV, and *3*) the use of oxygenation index to define severity. In addition, an "at-risk" categorization was established to guide early identification of children with hypoxemic respiratory failure. The recently published PARDS Incidence and Epidemiology study found that PARDS was present in 3% of patients admitted to pediatric intensive care units, with a mortality of 17% (2).

Noninvasive Respiratory Support

NIV has gained popularity for acute hypoxemic respiratory failure, including in bronchiolitis and pneumonia. Noninvasive support includes continuous positive airway pressure (CPAP), bilevel positive airway pressure, and heated humidified HFNC. Trials in bronchiolitis have suggested a tiered approach, with nasal cannula sufficient for most subjects and escalation to HFNC for those requiring additional support (3), with further escalation to CPAP for those failing HFNC (4). Although extrapolation to other causes of respiratory failure are less proven, an approach that proceeds from nasal cannula to HFNC to CPAP to bilevel positive airway pressure appears reasonable for most cases of pediatric hypoxemic respiratory failure. Because of concerns regarding prolonged excessive support, explicit weaning protocols should be instituted for stepwise reduction in all types of NIV.

Conventional Mechanical Ventilation

Children who are intubated on invasive ventilation should have tidal volume (V_T), peak inspiratory pressure (PIP), and positive end-expiratory pressure (PEEP) titrated to achieve oxygenation and ventilation goals while attempting to limit ventilator-induced lung injury. Despite a lack of evidence associating tidal V_T and mortality in pediatrics, V_T is generally set to 5–8 ml/kg of ideal body weight. As transpulmonary and plateau pressures are uncommonly measured in children, PIP is often used as a surrogate, and an association between PIP and mortality has been seen in pediatrics. The Pediatric Acute Lung Injury Consensus Conference recommends keeping PIP $\leqslant$28 cm H_2O, with allowance up to 32 cm H_2O in subjects with poor chest wall compliance (1). PEEP is commonly employed to maintain alveolar recruitment and improve oxygenation in pediatric hypoxemic respiratory failure. Minimal data exist regarding the optimal PEEP in children with PARDS or how to set this PEEP, but PEEPs of $\leqslant$15–18 cm H_2O have been reported. Observational data suggest that higher amounts of PEEP may be associated with improved outcomes (5). Ventilator weaning protocols and extubation readiness tests expedite ventilator discontinuation in adults and should be considered in children. Difficult-to-wean patients are a population requiring additional study.

Advanced Therapies

Despite a paucity of evidence for efficacy, high-frequency oscillatory ventilation and other nonconventional ventilator modes, such as airway pressure release ventilation, remain common rescue therapies for severe PARDS with sustained or refractory hypoxemia (6). Other adjunctive therapies for hypoxemia include corticosteroids, inhaled nitric oxide, prone positioning, and neuromuscular blockade. Specific pediatric evidence supporting efficacy for any of these therapies does not currently exist, and the use of each therapy should be considered on an individual basis, depending on center expertise. Venovenous extracorporeal membrane oxygenation (ECMO) is an increasingly employed salvage therapy for severe hypoxemia. Controversy remains as to the appropriate time for the initiation of ECMO as well as to which pediatric patients are good candidates. In general, adjunctive therapies used for refractory PARDS should be discontinued before ventilator weaning and extubation readiness testing. Some therapies, such as corticosteroids for PARDS, require weaning themselves, which can be performed alongside ventilator weaning.

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HOME FIRES, WILDFIRES AND MORE: AN UPDATE ON SMOKE INHALATION LUNG INJURY

John R. Balmes

Smoke from structural fires is a mixture of particles of various sizes and irritant gases (1). The particles usually have carbon cores with complex hydrocarbons on their surface, such as toxic polycyclic aromatic hydrocarbons. Carbon monoxide is always present. When modern buildings filled with synthetic materials burn, the products of combustion are also often toxic, including hydrogen cyanide, formaldehyde, acrolein, hydrogen chloride, phosgene, dioxin, and metals.

Smoke Inhalation from Structural Fires

Airway injury from smoke inhalation depends on the composition of the smoke and the duration of the exposure (2). Although the upper airway can suffer both direct thermal injury and chemical injury, the lower airway (below the vocal cords) is injured by direct chemical effects only. Obstruction of the upper airway is a potentially life-threatening complication of both thermal and chemical injury to the larynx. Lower airway obstruction from toxic bronchitis/bronchiolitis can also be severe. Bronchospasm and airway casts of mixed debris (exfoliated epithelium, inflammatory cells, protein-rich exudation, and mucus) can lead to hypoxemia, atelectasis, and altered hemodynamics. Injury to the lung parenchyma due to chemical pneumonitis can be severe enough to cause acute respiratory distress syndrome. Secondary bacterial infection is also common.

When feasible, fiberoptic bronchoscopy should be performed to assess smoke inhalation injury of the upper and lower airways (2). Chest computed tomography findings of bilateral opacities, a decreased arterial oxygen tension/fraction of inspired oxygen ratio (<300 mm Hg on a minimum of 5 cm H_20 PEEP), carboxyhemoglobin level on admission (>20%), and airway neutrophilia on bronchoalveolar lavage (>20%) are indicators of the severity of smoke inhalation. Repeated bronchoscopy with lavage can remove obstructing debris. Efforts to mobilize secretions with mucolytics, frequent turning, chest physiotherapy, and bronchodilator treatment can also be used. Frequent sputum cultures to monitor for bacterial infection are recommended, but prophylactic antibiotics are not.

Figure 2. Family wearing N95 masks in Los Angeles during the Thomas Fire in December 2017.

Effects of Poor Air Quality Due to Wildfire Smoke on Children's Respiratory Health

Climate change has increased the danger of catastrophic wildfires around the globe (3). The composition of wildfire smoke depends on the fuel type, temperature of the fire, and wind conditions. Fine particulate matter is the principal pollutant of health concern in wildfire smoke for short-term exposures (hours to weeks). In children, exposure to fine particulate matter is associated with exacerbations of asthma and increased incidence of acute lower respiratory tract infections. Recent literature shows a strong association between wildfire smoke exposure and increased respiratory morbidity (4, 5).

Approaches to the Reduction of Children's Exposure to Wildfire Smoke

The National Institute for Occupational Safety and Health certifies that N95 masks filter at least 95% of airborne particles ≥0.3 microns if fitted properly (Figure 2). These masks have not been certified for use in children. In addition, wearing a mask may provide a false sense of security and result in children participating in activities outdoors that may result in increased exposure. Recommendations to reduce exposure to wildfire smoke include *1*) keep children indoors as much as possible with the doors and windows closed, *2*) if available, use a central ventilation system to filter the air by running it with the fresh-air intake closed (recirculate mode), and *3*) use high-efficiency particulate air filters when available to reduce particle levels in a single room (3).

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VAPORIZERS, E-CIGARETTES, AND OTHER ELECTRONIC DELIVERY SYSTEMS: TOBACCO AND BEYOND

Alicia Casey and Alexandra Kass

U. S. adolescent cigarette use has substantially decreased over the past 20 years with only 3.6% of high school seniors currently smoking cigarettes, down from 24.6% in 1997. (1) This constitutes a major public health triumph, as most adult smokers begin smoking before the age of 18 years. Unfortunately, millions of dollars spent on marketing to adolescents (2) has reversed past progress and resulted in an increase in e-cigarette use with 27.5% of high school students using in 2019 (3). Respiratory complications associated with e-cigarette use are rapidly emerging, with e-cigarette and vaping use–associated lung injury (EVALI) becoming a public health epidemic. EVALI has led to more than 2,500 hospitalizations and 55 deaths in the United States from August through the end of 2019 (4).

The current e-cigarette market is largely unregulated, with none of the available devices approved by the U.S. Food and Drug Administration. Most devices consist of a battery, a heating element, and a cartridge or pod containing the e-cigarette liquid ("e-liquid") that is vaporized. There are varying components to e-liquids, but they are typically comprised of psychoactive agents (nicotine or tetrahydrocannabinol) and solvents used to dilute the liquid to a concentration that allows vaporization (5). Flavorings are frequently added to increase palatability and appeal to adolescents. The safety of these inhaled flavorings is largely unknown. One commonly used flavor is diacetyl (2,3-butanediol), which is known to be associated with bronchiolitis obliterans (6). Finally, additional thinning or thickening agents are frequently added to maintain a desired viscosity. Vitamin E acetate, a commonly used thickening agent, has been strongly associated with EVALI (7).

Both primary and secondhand exposures have already been associated with pulmonary complications. The most urgent known respiratory complication associated with vaping is EVALI, which is characterized by respiratory symptoms and pulmonary infiltrates on imaging in a patient who has used vaping products in the previous 90 days. This is a diagnosis of exclusion in the absence of infection or other explanation (7). The spectrum of EVALI symptoms range from minor cough and shortness of breath to respiratory failure with hypoxia. Gastrointestinal and systemic symptoms are also common. The U.S. Centers for Disease Control recommends that patients with oxygen saturation <95% and/or respiratory distress be admitted and that outpatients be followed closely within 24–48 hours of presentation, as clinical status can evolve rapidly (8). Chest imaging often reveals multifocal opacities and can show evidence of both airway and alveolar disease. A wide range of pathologic findings consistent with toxic chemical lung injury have been reported, including lipoid pneumonia, hypersensitivity pneumonitis, eosinophilic pneumonitis, diffuse alveolar damage, and diffuse alveolar hemorrhage (9). Treatment involves supportive care and the cessation of e-cigarette use, with reports of good response to corticosteroids (10).

There have been tremendous advocacy efforts by both the American Academy of Pediatrics and the American Thoracic Society aimed at limiting the scope of the youth vaping epidemic. The pediatric pulmonary community must amplify these efforts to prevent further increases in e-cigarette use among youth and associated respiratory complications.

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PULMONARY COMPLICATIONS OF SARCOIDOSIS

Andrew T. Barber and Timothy J. Vece

Sarcoidosis is a rare granulomatous disease with a variable presentation that affects multiple organ systems, with an incidence of 0.3–1.2 per 100,000 children (1–3). The cause of sarcoidosis is unknown; however, it is likely due to an exaggerated immune response triggered by an environmental antigen in genetically susceptible individuals. Diagnosis requires clinical, radiographic, and histologic evidence as well as evidence of systemic disease (4). Importantly, other causes of granulomatous diseases, such as mycobacterial infection, must be excluded.

Presentation

Multiple organ systems may be involved in sarcoidosis, including the lungs, lymph nodes, skin, eyes, liver, and spleen. In older children and adults, the lungs are most commonly affected (>90%) (5), but in younger children, the lungs are

less frequently involved (22% in children <4 yr) (2). When the lungs are involved, patients may present with cough or dyspnea; however, it is also possible to have histologic evidence of lung involvement with no respiratory symptoms. The majority of children (78%) have nonspecific symptoms, including fever, fatigue, and weight loss (6). The variation in symptoms makes sarcoidosis difficult to diagnose.

Imaging, Ancillary Testing, and Histology

Chest radiographs are important for staging disease. They may show hilar adenopathy and/or parenchymal opacities. Chest computed tomography has become more important over time for revealing the extent of disease and often reveals ground-glass opacities, septal thickening, hilar and/or mediastinal adenopathy, and peribronchovascular and pleural nodules. Bronchoscopy is often normal but may show an increase in lymphocytes with an elevated CD4/CD8 ratio. Pulmonary function testing can reveal a restrictive pattern with a low diffusion capacity. Serum angiotensin converting enzyme has been used for diagnosis; however, it is not sensitive and is best used for monitoring disease activity. Histopathology shows noncaseating granulomas with central follicles of epithelioid cells and $CD4^+$ lymphocytes surrounded by a ring of loosely packed $CD4^+$ and $CD8^+$ lymphocytes.

Staging/Treatment

Staging is based on chest radiograph findings, and the most commonly used system is the Scadding classification, which was first described in adults but has since been applied to children (1, 3, 7) (Table 1). Chest radiographs may miss the degree of pulmonary fibrosis; therefore, chest CT imaging is used to assess extent of disease in all patients. The main goals of therapy are to improve symptom burden and prevent end organ damage. Treatment recommendations in pediatrics generally follow adult recommendations (Table 2). Up to 50% of adult patients do not manifest symptoms of disease, and 30% spontaneously resolve; therefore, treatment is not recommended unless there is progressive disease or involvement of susceptible tissues, such as neural or cardiac disease (5). First-line therapy is systemic corticosteroids, usually 1–2 mg/kg/d. If long-term treatment is needed or if symptoms are refractory to initial treatment, steroid-sparing agents, such as methotrexate or azathioprine, are used. Treatment should be given in conjunction with a rheumatologist, as there are no randomized controlled studies in children.

Table 1. Scadding staging of pulmonary sarcoidosis in adults based on chest radiographic findings

Stage	Findings
0	Normal chest radiograph
I	Hilar lymphadenopathy alone
II	Hilar lymphadenopathy with parenchymal involvement
III	No hilar involvement with parenchymal involvement
IV	Signs of fibrosis

Table 2. Treatment options for pulmonary sarcoidosis

Presentation	Treatment
No symptoms* and Scadding stage 0–II	Observation
Significant symptoms or Scadding stage III–IV	First-line
	Systemic corticosteroids 1–2 mg/kg/d
	Second-line
	Methotrexate†
	Azathioprine†
	Leflunomide†
	Mycophenolate mofetil†
	Third-line
	Infliximab†

*Note that this table applies specifically to pulmonary involvement/symptoms. Immediate treatment, regardless of pulmonary disease, is indicated with certain organ involvement, such as neurologic, cardiac, or eye disease.
†Dosing should be discussed with a pediatric rheumatologist.

(Table 2). Infliximab, a TNFα (tumor necrosis factor α) inhibitor with antigranulomatous properties, is used in refractory disease (5).

Conclusions

Sarcoidosis is a rare disease in pediatric patients. Diagnosis is difficult and relies on multiple diagnostic modalities. As spontaneous disease resolution is common, care must be taken when initiating therapy, and careful follow-up for both progression and relapse is required. A multicenter approach will be required to further improve our understanding and treatment of sarcoidosis in children.

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PULMONARY COMPLICATIONS OF CONGENITAL HEART DISEASE

Gregory Montgomery and Ryan Serrano

Interdependence between the cardiac and pulmonary systems is such that the disruption of one has a profound impact on the other. This review highlights the importance of the cardiopulmonary relationship in the context of common respiratory complications seen in children with congenital heart disease (CHD).

Presence of airway abnormalities can limit respiratory efficiency in children with CHD. Extrinsic tracheal compression can occur with vascular abnormalities, including vascular ring or pulmonary artery sling (Figure 3 and Video 1) (1). Tetralogy of Fallot with absent pulmonary valve leaflets is associated with aneurysmal dilatation of main and branch pulmonary arteries, which may compress the central airways. Compressive vascular abnormalities are often undetected unless there is a high index of suspicion in patients with asymmetric air trapping, persistent monophonic wheezing, or other inexplicable need for high-level respiratory support. Interventions, including aortopexy, tracheopexy, and pulmonary artery reduction, may be considered but may not provide long-term symptomatic relief.

Hypoplastic left heart syndrome with intact atrial septum prevents the escape of blood from the left side of the heart, leading to significant elevation in pulmonary venous and arterial pressures, severely dilated lymphatics, and "arterialization" of pulmonary veins. Despite immediate postnatal and/or fetal intervention, severe hypoxemic respiratory failure and severe, often irreversible, pulmonary vascular changes may impede successful single ventricle palliation and, at worst, result in neonatal death (2).

Video 1. Flexible bronchoscopy: left mainstem bronchus compression.

Children with Fontan physiology may see physiologic limitation and even accelerated demise because of intervening pulmonary issues. Respiratory complications may include lymphatic congestion and pulmonary edema, pleural effusions, and plastic bronchitis. Symptoms may manifest as chronic cough or increased work of breathing or more profoundly as hypoxemic respiratory failure, acute life-threatening airway obstruction, and death. In addition, flow distribution abnormalities in Fontan physiology because of presence of aortopulmonary collaterals and/or pulmonary artery hypoplasia as well as the presence of lower, nonpulsatile flow can hasten the development of pulmonary vascular disease through acquired endothelial dysfunction (3).

Early diagnosis and treatment of CHD has decreased the incidence of late onset, irreversible pulmonary hypertension associated with systemic-to-pulmonary artery shunts (e.g.,

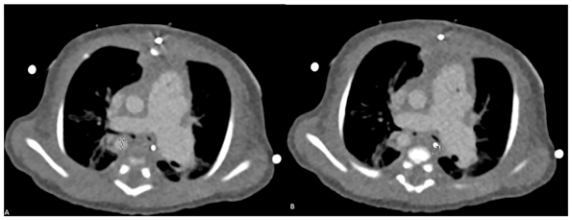

Figure 3. Computed tomographic chest imaging in a patient with Tetralogy of Fallot and absent pulmonary valve. (*A*) Severe compression of the right mainstem bronchus between the right pulmonary artery and descending right-sided thoracic aorta. (*B*) Severe compression of the left main bronchus between the left pulmonary arterial aneurysm and esophagus.

Table 3. Medical and procedural interventions for pulmonary hypertension*

Pharmacotherapy	Indication	Adverse Effects
Calcium channel blocker	Acute vasoreactivity responders†	Bradycardia, edema, constipation, and decreased CO
Amlodipine	—	—
Nifedipine	—	—
PDE-5 inhibitor	First-line pulmonary hypertension therapy	Headache, congestion, flushing, hypotension, and priapism
Sildenafil	—	—
Tadalafil	Greater than 3 yr of age	—
Prostacyclin	Severe pulmonary hypertension, high-risk patients	Flushing, jaw pain, headache, diarrhea, and hypotension
Treprostinil (subcutaneous)	—	Site pain and cellulitis/infection
Treprostinil (inhaled)	—	Worsening reactive airway disease
Treprostinil (oral)	—	GI side effects
Epoprostenol (intravenous)	—	Central line complications
Iloprost (inhaled)	—	Worsening reactive airway disease
Selexipeg (oral)	Not FDA approved for pediatric pulmonary hypertension	—
Endothelin receptor antagonist	Moderate to severe pulmonary hypertension	Hepatotoxicity, teratogenicity, fluid restriction, and anemia
Bosentan	—	—
Ambrisentan	Not FDA approved for pediatric pulmonary hypertension	—
Macitentan	Not FDA approved for pediatric pulmonary hypertension	—
Soluble guanylate cyclase stimulator	—	—
Riociguat	Chronic thrombomebolic pulmonary hypertension	Hypotension, peripheral edema, headache, and GI symptoms
Vitamin K antagonist	—	—
Warfain	IPAH/HPAH	Bleeding and hemorrhage

(continued on following page)

Table 3. Medical and procedural interventions for pulmonary hypertension* (continued)

Surgical/Percutaneous Intervention	Indication	Description	Adverse Effects
Pott's anastomosis	Suprasystemic pulmonary pressures	Surgical creation of an unrestrictive anastomosis between the LPA and the descending aorta	Surgical death and chronic lower body desaturation
Atrial septostomy/ septectomy	Severe pulmonary hypertension, failure of medical treatment	Surgical or percutaneous creation of an atrial septal defect to increase CO and O_2 delivery	Procedural complication
Lung transplantation	Severe pulmonary hypertension, failure of medical treatment	—	Transplant complications (death, rejection, and infection)
Pulmonary vein angioplasty/stent	Pulmonary vein stenosis	Percutaneous balloon angioplasty or stenting of stenotic pulmonary vein(s)	Procedural complication
Mitral valvuloplasty/ replacement	Congenital mitral valve stenosis	Percutaneous balloon angioplasty, surgical valve repair, or valve replacement	Procedural complication
Aortic valvuloplasty/ replacement	Critical aortic stenosis	Percutaneous balloon angipolasty or surgical valvotomy	Procedural complication

Definition of abbreviations: CO = cardiac output; FDA = U.S. Food and Drug Administration; GI = gastrointestinal; HPAH = hereditary pulmonary artery hypertension; IPAH = idiopathic pulmonary artery hypertension; LPA = left pulmonary artery; PDE = phosphodiesterase.
*For details about classification of low- versus high-risk patients, please see the American Heart Association guidelines (8) for pediatric pulmonary hypertension.
†Acute vasoreactive responders are defined as patients with a decrease in mean pulmonary artery pressure >20%, an increase or no change in cardiac index, and a decrease or no change in pulmonary vascular resistance to systemic vascular resistance ratio when challenged with inhaled nitric oxide (20–80 ppm) and 100% oxygen during cardiac catheterization.

ventricular septal defects, atrial septal defect, and patent ductus arteriosus). However, certain at-risk populations (e.g., those with Down's syndrome, extremely premature infants, and those with moderate to severe chronic lung disease) should be considered for early surgical repair, as a large volume overload on the lungs can worsen chronic lung disease and accelerate the development of pulmonary hypertension (4,5). Pulmonary hypertension remains a significant cause of morbidity and mortality in other forms of CHD, including mitral stenosis, pulmonary vein stenosis, truncus arteriosus, transposition of the great arteries, and obstructed anomalous pulmonary venous return (4). Medical pulmonary hypertension management has improved dramatically, and surgical techniques such as Pott's shunt, which creates an anastomosis between the left pulmonary artery to the descending aorta, are being performed successfully in cases of sustained suprasystemic pulmonary hypertension (Table 3) (5, 6).

Pulmonary complications as direct sequelae of CHD-related surgery must also be considered. Vocal cord paresis and diaphragmatic paralysis are potential complications of any mediastinal surgery. Unexpected thoracic duct ligation or injury can cause chylothorax or pulmonary lymphatic congestion. Some data suggest that sternotomy and cardiopulmonary bypass may lead to notable reductions in forced vital capacity and lower expiratory reserve over time (7).

The physiologic and anatomic disruption of the cardiovascular system in patients with CHD has a direct and long-lasting impact on the pulmonary system. Practitioners should be aware of these complications and strive to implement the most up-to-date approaches of diagnosis and management.

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UPDATES AND MANAGEMENT OF CONGENITAL DIAPHRAGMATIC HERNIA

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Epidemiology and Pathophysiology

Congenital diaphragmatic hernia (CDH) occurs in 1:3,000 live births (1). Eighty percent of cases are left-sided defects, and 20% are right-sided defects. Bilateral defects are rare (2). Bochdalek hernias are a defect in the posterior lateral portion of the diaphragm, whereas Morgagni hernias affect the central anterior portion.

CDH is likely result of failure of the pleuroperitoneal canals to close at the end of the embryonic period or may be a primary disturbance of mesenchymal–epithelial interactions resulting in abnormal diaphragmatic development and pulmonary epithelial branching (2). Mass effect on the ipsilateral lung results in pulmonary hypoplasia. Normal bronchial and vascular branching patterns are disrupted, leading to increased pulmonary vascular resistance and pulmonary hypertension.

Diagnosis and Prognosis

The majority of CDH cases in the United States are diagnosed by prenatal ultrasound

and can be confirmed by additional imaging, such as CT imaging and magnetic resonance imaging (1). Parameters such as the lung:head ratio, observed-to-expected lung:head ratio, and liver herniation help predict morbidity and mortality. Liver herniation into the left chest is a poor prognostic factor and is highly predictive of the need for ECMO and increased mortality (3). Other determinants of outcome include prenatal diagnosis (4), prematurity (5), and associated major malformations (4).

Fetal Intervention

Prenatal interventions include maternal antenatal corticosteroid administration and fetoscopic endoluminal tracheal occlusion. Interventional studies have been limited by small sample size, and insufficient evidence exists to suggest that fetoscopic endoluminal tracheal occlusion should be implemented in routine clinical practice (6).

Postnatal Management

Postnatal CDH management includes delivery at a center with immediate access to neonatology, pediatric surgeons, and ECMO capabilities. Minimizing stress that can induce pulmonary hypertensive crises is crucial. Early intubation with avoidance of bag mask ventilation, gastric decompression, and gentle lung ventilation are mainstays of treatment immediately after birth. Surgical repair should be attempted once the child is hemodynamically stable (1). Additional recommendations are summarized in Table 4 (7).

Long-Term Complications

Survival rates at tertiary centers have improved to 70–92% with improvement in management (8). This has created a unique cohort of children, adolescents, and adults with complex medical needs (9). Long-term complications include persistent pulmonary hypertension, neurodevelopmental impairment, sensorineural hearing loss,

Table 4. Recommendations for postnatal management based on systematic review of the literature

Intervention	Recommendation	Grade	Class of Evidence
Mode of mechanical ventilation	Gentle conventional ventilation with permissive hypercapnia	C	III–IV
iNO	Cannot be recommended for routine use	C	II
Other medical adjuncts (sildenafil, milrinone, prostacyclin, PgE_1, and Bosentan)	Minimal evidence to support use	D	IV
Prenatal glucocorticoids	Provides no benefit	B–C	II–III
Postnatal glucocorticoids	Provides no benefit	D	IV
Mode of ECMO (VV or VA)	No survival advantage to either, but VV preferred when possible due to less neurologic complications	C	III–IV
Minimally invasive surgery vs. open surgery	Open repair led to significantly fewer recurrences	C	II–III
Type of patch	Polytetrafluoroethylene was most durable	C	IV

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; iNO = inhaled nitric oxide; PgE_1 = prostaglandin E_1; VA = venoarterial; VV = venovenous.

gastroesophageal reflux disease, small bowel obstruction, scoliosis, and diaphragmatic hernia recurrence (9).

Pulmonary Morbidity

Pulmonary hypoplasia and pulmonary hypertension, hallmarks of CDH, are associated with disease severity (10). The incidence of pulmonary hypertension after hospital discharge is 10–20% (9). Although severe pulmonary hypertension can persist throughout infancy, longitudinal studies demonstrate eventual resolution in many (11).

Wheezing within the first 2 years of life, significant rates of inhaler use, asthma, lower lung function, ventilation/perfusion mismatch, and decreased exercise endurance are observed at higher rates compared with healthy control subjects (9).

Long-Term Multidisciplinary CDH Care

The 2008 American Academy of Pediatrics consensus statement recommends periodic follow-up by a multidisciplinary team (including pediatric surgery, neonatology, cardiology, pulmonology, gastroenterology, and dieticians, among others) (12). A recent review by the CDH EURO Consortium reaffirms this view and is working on standardizing care (13).

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

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