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In this update on pediatric pulmonary medicine, we have selected several studies from many outstanding publications from the *American Journal of Respiratory and Critical Care Medicine*, the *American Journal of Respiratory Cell and Molecular Biology*, and the *Annals of the American Thoracic Society* in 2020 to provide readers with an overview of the important contributions across the field of pediatric respiratory medicine. We have selected papers related to cystic fibrosis (CF), primary ciliary dyskinesia (PCD), neonatal and developmental lung diseases, asthma, sleep, noninvasive ventilation, and adverse environmental impacts on childhood lung function. To minimize overlap with other updates, articles related to pediatric critical care and childhood factors associated with adult asthma outcomes are included within the Critical Care and Adult Asthma reviews.

CF and PCD

Diagnosis

Whole-gene sequencing of the *CFTR* (CF transmembrane conductance regulator) gene has had implications for newborn screening protocols and first-line targeted mutation analysis. An intronic variant (c.3874–4522A>G in intron 23), common in those with incomplete genetic diagnoses, was estimated to occur in ∼2.2% of the United Kingdom population with CF (1); these findings are consistent with an earlier French study (2). Exome sequencing, used in some diagnostic protocols of PCD, is also furthering our understanding of cilia biology (3). A *CFAP300* mutation was identified in 3.6% of patients with PCD of unknown cause in Slavic populations, supporting the utility of population-specific testing in that group (4). The presence of pseudogenes has hampered genetic identification of pathogenic *HYDIN* variants to date (5); this was recently addressed by the description of coexisting deficiency in ciliary *SPEF2* detected using immunofluorescence (6).

Early Lung Disease

Clinical interest in multiple breath washout (MBW) is growing, with technique-specific recommendations starting to appear in CF-related management guidelines (7). The greater sensitivity of MBW to detect early impairment during periods of apparent clinical stability as compared with spirometry has been recently recognized. Perrem and colleagues described greater sensitivity than spirometry to detect functional impairment during acute respiratory events in school-aged children with CF (8), expanding earlier findings in children of preschool age (9) and further underscoring its clinical utility. In this setting, the combined assessments of lung clearance index (LCI) and FEV_1 were complementary, as together, these modalities identified more events (54%) than either metric alone. In PCD, MBW also offered better sensitivity as compared with spirometry for the detection of early lung disease during clinic stability, yet the added benefit of spirometry was shown in these subjects, as spirometry-based obstruction was worse in PCD than CF despite similar measurements of LCI (10). Expanding collaborative multicenter approaches to generate larger PCD cohorts should be an important focus for future research, as this will likely improve our understanding of differences in pathophysiology, enable comparison of treatment response between PCD and CF, and further characterize PCD subtypes (11).

Advanced imaging techniques hold promise to further optimize the identification of early lung disease in children in addition to assessments of lung function by MBW and spirometry. Thomen and colleagues described the ability of magnetic resonance imaging (MRI) to provide structural and functional information, using ultrashort echo MRI and hyperpolarized ^{129}Xe (12), respectively, providing an important imaging-based approach to explore structure–function relationships. MRI has also increased our

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understanding of sinus development and CF-related chronic rhinosinusitis evolution (13): Infants and preschoolers with CF had similar paranasal sinus dimensions as healthy control subjects, but a high prevalence of paranasal sinus abnormalities were identified as starting from infancy. This imaging strategy will likely provide an important platform for future work to better understand interplay between chronic rhinosinusitis and early lung disease development.

Infection

The tenet that chronic *Pseudomonas aeruginosa* colonization replaces *Staphylococcus aureus* over time in CF has largely been based on cross-sectional registry data that lacks quantitative tracking of bacterial abundance (14). In a study of serial longitudinal sputum cultures over a 13-year period, however, this pattern was rarely observed. Instead, there was a trend toward the concurrent accumulation of both species over time. Concerns regarding the generalizability of these findings (14) were partly addressed by United Kingdom data confirming coinfection was common and sustained with advancing age (15). Long and colleagues presented impressive whole-genome sequencing data describing evolutionary biology across ∼1,400 isolates within a cohort of 246 pediatric subjects with CF from five geographically distant CF centers over 2 years (16). *S. aureus* had "an open pangenome indicating ongoing flow of new genetic elements," with adapted changes in genes related to persistence and antimicrobial resistance that developed during infection with bouts of antibiotic treatment. Strain sharing occurred through exposures in common households as well as from clinical providers moving between CF care centers. A Perspective article summarized current concerns regarding limitations of current antibacterial treatments (17). By significantly reducing *P. aeruginosa* susceptibility testing, significant cost savings were achieved without affecting acute exacerbation outcomes (18). Moreover, administration of nebulized antibiotics in addition to intravenous antibiotics conferred no further benefit in CF, although selection bias is an important caveat when interpreting retrospective registry-based analyses (19).

The pathogenicity of *Aspergillus* species in the absence of allergic sensitization remains an ongoing debate. The recent longitudinal AREST-CF (Australian Respiratory Early Surveillance Team for CF) study described greater rates of chest computed tomography (CT) scan abnormalities at the time of *Aspergillus* infection and greater subsequent progression, with incremental worsening in end-of-study lung disease for each additional time isolated (20). These structural findings echo those from other cohorts (21) and are likely clinically relevant given the utility of CT to predict long-term functional outcomes (22). Proving causality will require well-designed clinical trials, as *Aspergillus* may also reflect more aggressive antibiotic treatment of other known pathogens (23–25).

Immune responses may be suppressed in CF (26). *In vitro* application of CF plasma on peripheral blood mononuclear cells (PBMCs) led to altered mRNA/microRNA expression and blunted immune responses (27). Circulating CF leukocytes exhibited dysfunctional inflammatory responses to bacterial antigens, with decreased NF-κB (nuclear factor-κB)–mediated induction of inflammatory genes (28). Antiviral activity of airway surface liquid was also impaired in nasal/tracheal fluid from newborn CF pigs (29), possibly because of fluid pH differences (30).

CFTR Modulators

The successes in CFTR modulator clinical trials offer exciting potential to benefit ∼90% of the population with CF (31, 32). Recent publications have explored questions regarding CFTR modulator use in younger age groups, which included questions regarding important response heterogeneity, initial real-world experience of approved modulators, and novel benefits (33–36). Encouraging safety data and biomarker response (e.g., sweat chloride) for ivacaftor in 25 infants (33) formed the basis for recent regulatory approval in ages ⩾4 months.

The effect of sex on ivacaftor response was described in a *post hoc* analysis of GOAL (G551D Observational) study data (34). Although FEV_1 response had not previously shown sex differences (37), females had better short-term responses in sweat chloride and exacerbation frequency. Hutchison and colleagues described the successful discontinuation of pancreatic enzyme replacement therapy after ivacaftor therapy (35), illustrating the potential for treatment burden reduction, an important priority for the CF community (38), and adding to the known extrapulmonary effects of CFTR modulators (39). Real-world data have provided additional insights regarding CFTR modulator therapies. In a large French multicenter study, patients with portal hypertension or cirrhosis—typically excluded from clinical trials—tolerated lumacaftor–ivacaftor well, whereas adolescents—often underrepresented within trials—had a more gradual response but achieved a greater peak effect than adults (36). Studies of response heterogeneity support a personalized approach to CFTR therapy, ideally based on robust biomarkers. Whether organoids provide this tool remains unclear, as initial promising findings (40) were not replicated in recent data; there was no correlation between organoid swelling and clinical response, including LCI (41), in cohorts receiving ivacaftor (41) or lumacaftor–ivacaftor (42).

Whereas human data reported no changes in microbiome or sputum inflammation in subjects treated with ivacaftor (43), several preclinical studies have investigated CFTR modulator therapy benefits using *in vitro* models. In PBMCs from patients with CF, ivacaftor altered genes related to infection, inflammation, and metabolism (44) and, importantly, identified transcriptomic patterns that predicted clinical responsiveness (45). CF animal models, which now include small animals, may be well suited to investigate effects on chronic inflammation, airway infection, and other long-term effects (46). In the CF rat, ivacaftor normalized mucous abnormalities, increasing airway surface liquid depth, reducing mucous viscosity, and improving mucociliary transport (47). The accumulation of IFT88 protein in the ciliary base region in CF cells normalized with ivacaftor treatment (48), suggesting that CFTR dysfunction may affect ciliary function.

Other Medications

Existing antiinflammatory agents may play an important role in CF management. CF registry data have provided insight into the long-term benefits of azithromycin, including slower annual FEV_1 decline over 3 years in patients with chronic *P. aeruginosa* in the CF Foundation registry (49) and over a 5-year period in children—but not adults—in the French CF registry after correction for baseline *P. aeruginosa* status (50); the French data also showed fewer intravenous antibiotic–treated exacerbations. Separate CF Foundation registry analyses showed evidence for antagonism between azithromycin and tobramycin, including lack of benefit in annual FEV_1 decline (49) and worse outcomes for acute exacerbations treated with intravenous tobramycin on concurrent azithromycin (51). The results of an ongoing randomized

placebo-controlled trial (NCT02677701) may provide more insight (52).

The potential targets for antiinflammatory agents in CF may be broader than previously believed. In CF, increased airway smooth muscle (ASM) mass and impaired β-adrenergic–induced relaxation was described in the presence of IL-13 (53). Inflammation-induced decreases in β-adrenergic relaxation may contribute to airway hyperresponsiveness (54). Enhanced ASM mass and ASM responsiveness mediated by TGF-β and PI3 kinase signaling was also described in CF mice (55, 56).

Future Medications

Candidate therapeutic targets include modulators of other membrane ion transporters that influence CFTR function. Losartan restored voltage-dependent K^+ channel function to improve mucociliary transport, decrease mucous plugging, and indirectly decrease inflammation (57). Pendrin is an anion exchanger, which interacts with CFTR, in mediating ion transport and fluid secretion from airway epithelium (58). IL-4 pretreatment augmented $HCO3^-$ secretion by pendrin, which in turn enhanced chloride secretion by wild-type CFTR (59). SLC6A14, an L-arginine transporter, augments residual channel function of F508del-CFTR through an NO/PKG-mediated mechanism (60). CFTR dysfunction leads to abnormal processing of membrane lipid sphingomyelin, ceramide accumulation, and inefficient management of infection and inflammation (61). This can be overcome by replacing deficient acid ceramidase (61), an established treatment for Farber disease (62).

Novel modulators may offer an important alternative for those ineligible for current CFTR-based therapies (63). Danahay and colleagues described the ability of TMEM16A potentiator ETX001 to enhance anion secretion through calcium-activated chloride channels that compensate for defective CFTR to improve mucociliary clearance (64) while avoiding the intracellular calcium effects of its predecessors that inadvertently stimulated mucin secretion (63). Individuals with nonsense CFTR mutations may activate the nonsense-mediated RNA degradation pathway and limit CFTR expression. Nonsense-mediated RNA degradation pathway suppression in cells with CFTR W1282X mutations improved expression of the W1282X transporter, which possessed limited function (65). Mucociliary clearance can also be enhanced by an aerosolized product (ARINA-1) containing ascorbate, glutathione, and bicarbonate. On homozygous pF508.del bronchial epithelium, ARINA-1 alone, and in combination with CFTR modulators, decreased mucus viscosity (66).

An optimal approach to CF therapy would increase expression of the normal CFTR gene in airway epithelium (67, 68). The administration of adeno-associated virus expressing CFTR in CF pigs normalized transepithelial chloride current, airway surface pH, and viscosity (69). This approach in airway progenitor cells could lead to persistent expression. Our understanding of the cell types expressing CFTR and their distribution within the airways (70) has advanced significantly in recent years. Single-cell RNA sequencing studies discovered the ionocyte, a new CFTR-rich pulmonary epithelial cell type (71); although comprising <1–2% of epithelial cells, these cells express >50% of CFTR transcripts (72, 73). Ionocytes are anticipated to become an important focus of CF research and an emerging therapeutic target. Finally, a series of publications have outlined methodological advances with beneficial effects on our search for future therapeutics: improved methods for culturing human bronchial epithelial progenitor cells from airways (74, 75); flow-cytometry methodology for isolating airway macrophages from CF sputum (76) and BAL (77); and novel detailed profiling of individualized airway immune cells in lung disease, using CF sputum single-cell RNA sequencing (78, 79).

Neonatal and Developmental Lung Disease

Neonatal Respiratory Failure

Advancing our understanding of the pathogenesis of meconium aspiration syndrome, *in vivo* changes in surfactant phospholipid composition and impaired surfactant function suggest that surfactant dysfunction may contribute to abnormal gas exchange (80). In a lamb model of persistent pulmonary hypertension (PH) of the newborn (PPHN), AMPK activation corrected mitochondrial defects and enhanced angiogenesis (81). Highlighting the importance of model development, distinct transcriptional responses in pulmonary artery (PA) endothelium were identified from the shunt model as opposed to a PA ligation model of PPHN (82). Aiming to improve management of meconium aspiration syndrome and PPHN, Rawat and colleagues sought to optimize oxygenation in a lamb model and demonstrated that while 95–99% O_2 saturation provided better brain oxygen delivery, targeting 90–94% led to lower lung oxidative stress (83). Mutations in the ABCA3 (ATP-binding-cassette-transporter-A3) gene constitute another cause of neonatal respiratory failure; lung epithelial cell lines expressing various ABCA3 mutants have been created, which will facilitate screening for pharmacological correctors (84).

Lung Growth and Development

Understanding the multifactorial modulators underlying lung growth and development in health and disease requires knowledge about cell types and their interactions as well as the impact of perinatal stress and postnatal factors. The Human Lung Cell Atlas Consortium and the pediatric LungMap project made important progress in mapping genomic and transcriptomic characteristics of lung cells in health, disease, and development (85–87). Recent studies have also examined Hippo signaling and the role of YAP/TAZ in endothelium (88) and epithelium (89, 90) in lung angiogenesis and regenerative growth. Environmental factors can also affect lung development, as prenatal exposure to electronic cigarette (e-cigarette) aerosols induced extracellular matrix remodeling that could predispose to pulmonary disease later in life (91, 92). Finally, *in utero* maternal IL-5 exposure increased airway epithelial innervation in the fetus, resulting in airway hyperreactivity in adulthood (93). Thus, developmental stresses can affect lung responses to allergens in the adult (94).

Numerous studies have demonstrated the presence of an extensive microbiome throughout the respiratory tree in normal and diseased lungs. However, the exact timing of acquisition of the microbiome and changes over time are poorly understood, especially regarding the interesting question of whether the fetal lung is sterile or acquires its microbiome before birth. The presence of microbial DNA in human fetal lungs and placentas was recently reported as early as 11 weeks' gestation (95). Mechanisms underlying this observation are unknown, but transplacental transfer of microbial DNA is likely and may further influence development of the innate immune system.

Early-life risk factors impact growth and development of the lung across the lifespan; however, systematic studies to identify the

potential role of genes active during lung development as modulators of lung function in adults are uncertain. Using United Kingdom Biobank data, 55 genes, including those linked with developmental functions (96), were identified that were associated with airflow, suggesting a potential role of lung development genes as modulating adult lung function. Clear causal links remain unproven, however, and further studies linking identified genes with longitudinal changes of lung trajectory over time are needed (97).

Pathogenesis of Bronchopulmonary Dysplasia

The pathogenesis of bronchopulmonary dysplasia (BPD) is multifactorial and remains incompletely understood. It is clear that hyperoxia and mechanical ventilation can promote oxidative stress, inflammation, and cellular apoptosis; disrupt lung growth; and impair regenerative mechanisms (98). Insights into BPD pathogenesis have been explored in animal models, including hyperoxia or mechanical ventilation (99–101) and antenatal exposures to endotoxin or anti-VEGF drugs (sFlt-1) to mimic chorioamnionitis and preeclampsia, respectively (102–106).

Novel experiments from Zhang and colleagues suggest the potential role of autophagy as a cytoprotective mechanism in the hyperoxia mouse model of BPD and preterm baboons (99). Autophagic activity is induced in alveolar type II cells and macrophages during normal alveolarization but is impaired with hyperoxia. Other recent studies in experimental models of BPD induced by antenatal stress or postnatal hyperoxia further support the importance of preserving endothelial cell function, vascular growth, and angiocrine signaling. These studies present strong data that augmentation of HIF-1α (hypoxia-inducible factor-1α) signaling with HIF stabilizers before and after birth (102, 103), postnatal infusions of recombinant human insulin-like growth factor-1 (104, 105), and postnatal administration of vitamin D (106, 107) all sustain lung vascular and alveolar growth and prevent PH. Exposure of lung endothelium to hyperoxia was associated with detectable mitochondrial dysfunction that was exacerbated when fatty acid oxidation was suppressed (108). L-carnitine administration to hyperoxic newborn mice lessened lung injury and increased alveolarization, suggesting that fatty acid oxidation protects the developing lung from hyperoxia. Fetal ASM hyperoxia exposure was associated with senescence and secretion of inflammatory factors (109). Hyperoxia-induced senescence may thus increase susceptibility to airway disease later in life (110).

Normal lung development requires precise orchestration of airway, lung parenchymal, and vascular growth to achieve healthy lung structure and function. Disruption of lung vascular growth with preterm birth exerts a major impact on BPD risk and severity. Impaired production of proangiogenic factors, including VEGF-A (vascular endothelial growth factor A) as shown in experimental models and in the lungs of infants dying with BPD, suggests that therapies that support pulmonary vascular growth might aid growth of the distal lungs. FOXM1 and FOXF1 are downstream effectors of VEGF signaling, and administration of these effectors using novel nanoparticle delivery strategies improved lung structure and function after neonatal hyperoxic injury (100). Nanoparticle delivery of either FOXM1 or FOXF1 did not protect endothelial cells from apoptosis but increased endothelial proliferation and lung angiogenesis after the injury, improved elastin fiber organization, decreased alveolar simplification, and preserved lung function in mice reaching adulthood. These exciting findings demonstrate that delivery of proangiogenic transcription factors has promise as a therapy for BPD.

There is also significant interest in using mesenchymal stromal cells (MSCs) to treat BPD in the postnatal period (111–113). Compared with MSCs from term umbilical blood, hyperoxic lung MSCs exhibited decreased elastin deposition and impaired secretion of lung growth factors, whereas cord-derived MSCs still secreted these factors. Hyperoxia-treated lung MSCs may actually contribute to impaired lung growth (114, 115).

Severe BPD

Preclinical and clinical studies of BPD have highlighted the need to better understand antenatal factors that contribute to disease pathogenesis (116), better define the nature and patterns of severe disease (117–119), and elucidate the risk of late and adult disease (120–122). Failure to recognize distinct phenotypes of BPD, reflecting its multifactorial etiologies and comorbidities, has limited the development of more precise experimental models, clinical interventions, and clinical trial design. Advancing our understanding of severe BPD (sBPD), Wu and colleagues characterized the relative frequency of key physiologic features of the phenotype, including large airway disease, severe parenchymal disease, and PH (118). Each physiologic component alone did not fully convey the burden of sBPD; presence of all three components was the most common phenotype and was most strongly associated with outcomes such as death, tracheostomy, or the need for systemic pulmonary vasodilator at neonatal ICU discharge. PH was the primary predictor of mortality. Importantly, the severity of parenchymal lung disease on a CT scan did not independently correlate with any outcome evaluated. These results highlight the importance of BPD phenotyping for predicting outcomes and monitoring response to therapies, reflect the growing awareness of disease comorbidities that modulate BPD severity, and outline key evaluation steps that will likely allow for more precise care (119).

Advanced Imaging

Our ability to better assess and quantify BPD severity, progression over time, and treatment response remains limited in sBPD, which is characterized by heterogeneous lung regions with variable time constants owing to differing degrees of alveolar simplification, overdistension, atelectasis, fibrosis, and edema (117, 120–124). To understand this heterogeneity, Gouwens and colleagues investigated utility of end-inspiratory and end-expiratory MRI and determined the relative contribution of overdistended ("cystic") versus neighboring lung tissue to regional changes in V_T (121). "Cystic" areas contribute more to V_T than healthy areas when normalized for total lung volume and are not merely regions of trapped air but may even contribute to gas exchange. These findings suggest that advanced imaging may provide additional tools to improve clinical care via precision medicine in this challenging population.

Early pulmonary vascular disease (PVD) in preterm infants is associated with risk of sBPD, late PH, and late respiratory disease in childhood, but it is unclear whether echocardiography is an accurate tool for assessing PVD and cardiac performance in sBPD (124, 125). In addition to assessing airways and lung disease, MRI may offer noninvasive assessment of lung circulation and cardiac phenotype in sBPD, providing novel information beyond echocardiography alone. MRI can be used to determine left ventricular eccentricity index (MR-EI), main PA to aorta diameter ratio, pulmonary arterial

blood flow, and other indices in infants with sBPD and control subjects. MR-EI was associated with clinical features such as length of stay and duration of mechanical ventilation, and both increased PA/aorta and MR-EI were associated with the need for PH therapy during hospitalization and at discharge (123). Specific MRI may yield important useful metrics that correlate with disease severity and clinical outcomes in BPD.

Persistent Cardiopulmonary Disease in Adults Born Preterm

Growing literature has highlighted longer-term consequences of prematurity—with and without BPD—throughout adolescence and adulthood (126, 127). In a national longitudinal cohort of extremely preterm (EP) newborns assessed as 19 year olds (128) compared with control subjects, EP subjects had impaired lung function by spirometry, lower fractional exhaled nitric oxide, and impaired exercise capacity. A higher proportion had bronchodilator reversibility (27% vs. 6%), and all respiratory parameters were worse in the EP group with neonatal BPD.

In addition to persistent lung disease, young adults born prematurely have high rates of persistent PVD and PH with altered responsiveness to exercise (126, 127, 129, 130). Mulchrone and colleagues extended these observations by assessing right ventricular (RV)–PA coupling in this population to comprehensively assess hemodynamic coupling of RV with RV afterload owing to PA compliance (131). Analyzing measurements during right heart characterization and cardiac MRI, they reported evidence of high-resistance/low-compliance pulmonary vascular beds with attenuated RV adaptation in the face of increased vascular load. These findings suggest persistent RV systolic and diastolic dysfunction and decreased RV–PA coupling in an otherwise healthy cohort. Lung microvasculature changes were explored with dynamic contrast-enhanced MRI (130); male adults had measurable reductions in lung perfusion metrics, correlating with cardiopulmonary function. These findings further support the concept that perinatal injury and arrested growth associated with preterm birth cause persistent abnormalities in lung circulation and the cardiovascular system, highlighting the need for ongoing cardiopulmonary monitoring of former preterm infants throughout adulthood.

Asthma

Viral Infections and Asthma

Viral respiratory infections constitute an important risk factor for childhood asthma. Anderson and colleagues stimulated PBMCs *in vitro* with rhinovirus subspecies and described different patterns of response: Rhinovirus-A induced a stronger IFN-γ response, whereas rhinovirus-C induced a stronger eotaxin-2 response; children with asthma had lower responses to both viruses compared with control subjects but preserved T-helper cell type 1 (Th1) and Th2 patterns (132, 133). Although data on coronavirus disease (COVID-19) in pediatric asthma is still relatively scarce, we saw that pandemic-related measures implemented to reduce viral transmission have had marked effects on asthma-related presentations: Significant reductions were reported at a major U.S. pediatric hospital (134), even after adjusting for general hospital avoidance factors, echoing the findings from other institutions (135).

Genomics

Our understanding of the genomics of asthma continues to grow. Data from 462 children from CAMP (Childhood Asthma Management Project) showed seven microRNAs associated with FEV_1 response to budesonide (vs. placebo) (136, 137), including two (hsa-miR-155-5p and hsa-miR-532-5p) that were associated with dexamethasone-induced NF-κB levels in cell culture and predicted budesonide response (area under the curve, 0.86). This highlights the potential of using dynamic genomic data as biomarkers to predict clinical course and treatment response in asthma.

Obesity and Asthma

Insight into the complex—and likely heterogeneous—"obese asthma" phenotype was provided by several studies this year. The limitations of body mass index to characterize relationships or effects of obesity on asthma and lung function were illustrated by data from a large cohort of 5,421 children showing that—even after adjusting for body mass index—visceral fat measured by MRI was associated with higher asthma risk, higher FVC, and lower FEV_1/FVC ratio (138, 139). The exciting potential of using genomics (beyond genotype) in the study of asthma pathogenesis was nicely illustrated by Rastogi and colleagues. In an analysis of DNA methylation and gene expression in $CD4^+$ cells from children with asthma with and without obesity, they described significant differences in Rho-GTPase pathway genes, including *CDC42* (140, 141). *CDC42* silencing led to reduced expression of IFN-γ, indicating potential for Th1 polarization. Finally, in the search for early biomarkers and risk factors, birth cohort data from Chile (142, 143) focusing on the influence of maternal weight status on offspring outcomes described higher cord leptin levels in overweight mothers and 30% higher risk of positive Asthma Predictive Index for every 10 ng/ml increase in cord leptin. Leptin, a proinflammatory adipokine, has been implicated in obese asthma and may have utility as an early biomarker of asthma risk.

Respiratory Infections

Although effective vaccines or specific treatments for respiratory syncytial virus (RSV) remain lacking, research continues to elucidate host factors influencing disease that may present future targets. The traditional dogma that apoptosis pathways were used as defense mechanisms to limit viral spread was challenged: murine *in vitro* and *in vivo* data showed that RSV infection (in contrast to other viral infections) readily induces necroptosis (a proinflammatory apoptotic pathway) in airway epithelial cells (144). Inhibition of necroptosis-associated proteins reduced necroptosis and the pathological changes of RSV infection as well as ASM remodeling and development of experimental asthma in murine models (144). Questions remain regarding the validity of targeting necroptosis as a therapeutic strategy, including the exact mechanism by which RSV stimulates necroptosis and whether interfering with its inflammatory pathways may render children more susceptible to other infections (145). Severe RSV bronchiolitis is accompanied by distinct T-cell profiles (greater IL-4–expressing $CD8^+$ T-cell response) in infant nasal mucosal cells compared with milder disease (146), supporting previous murine model data outlining a pathogenic role for $CD8^+$ T cells (147). Increased T-cell *CD32* expression was documented in infants with severe RSV infections, suggesting it may represent a costimulatory pathway (148). Han and colleagues described a novel inhibitory role of CXCL4 (chemokine [C-X-C motif] ligand 4 or platelet factor 4) on RSV infection, replication, and disease via inhibition of RSV attachment to heparan sulfate on target cells

(149). CXCL4, through this competitive inhibitory mechanism, may offer a future alternative strategy for RSV prophylaxis (150). Highlighting the rapid pace of RSV vaccine research, a metanalysis of data from seven phase 1 trials of different intranasal live-attenuated vaccine candidates ($n = 241$ children 6–24 months of age) (151) demonstrated 50% efficacy in preventing acute respiratory illness and lower respiratory illness. A subset of "more promising" vaccines (which induced ⩾fourfold increase in neutralizing antibody titers in >80% recipients) produced sustained response, negating the need for reimmunization within the same RSV season. Encouraging safety and efficacy data suggests that live-attenuated RSV vaccines are well positioned for further stages of vaccine development (152) and eventually compete with other more advanced candidates such as nirsevimab (153).

Influenza A infections cause significant morbidity and mortality in children, and recent data have shown this is partly mediated through age-dependent differences in T-cell number, type, and localization (154). Allogenic hematopoietic cell transplant recipients are vulnerable to respiratory viral infections; one study found that nasal wash IL-4 levels were increased in this setting when challenged with viral respiratory tract infections (155). In children with viral respiratory tract infections, epithelial secretion of TSLP (thymic stromal lymphopoietin) increased; similar responses were observed in nasal epithelial cells treated with poly I:C, a synthetic analog of double-stranded RNA that mimics viral infection (156).

Sleep Medicine and Ventilatory Support

The effects of sleep-disordered breathing (SDB) on vascular aging and cardiovascular risk in adults are widely recognized, but there is building evidence of impact in childhood: Thrombin receptor-activating peptide and collagen antibodies, which play a role platelet aggregation, were significantly higher in both children with SDB (157, 158) and those with primary snoring (and normal apnea–hypopnea index) compared with control subjects. Recommendations to screen and treat early are further supported by the finding that longer SDB duration results in worse behavioral outcomes (159). Feasibility and effectiveness of screening efforts was aided by development and validation of a scoring system (SDBeasy) (159) and by the publication of normative data for home-based cardiorespiratory sleep monitoring in infants (160).

Dynamic technology offers exciting potential for noninvasive insight to inform clinical care in airway diseases (161). In an important proof-of-concept study, ultrashort echo time MRI and computational fluid dynamics analysis were used to quantify both airway narrowing severity and resultant functional increased work of breathing in infants with tracheomalacia compared with those without (162). Higher work of breathing was driven mainly by tracheal resistance, and energy expenditure was significantly reduced by continuous positive airway pressure (162).

To aid the process of starting noninvasive ventilation, the American Thoracic Society (ATS) Assembly on Sleep and Respiratory Neurobiology published a report focusing on the importance of mask selection on noninvasive ventilation effectiveness, comfort, and adherence (163). Future studies to aid mask selection should focus on individual anatomical variations using three-dimensional face mapping, nasal resistance measurements, and preferential flow route determination. There is a lack of evidence to guide decisions to initiate—or forgo—invasive or noninvasive long-term ventilation (164), but recent qualitative studies have provided insight. Families (all but one of which chose long-term ventilation) described the stress of making the decision and their desire for comprehensive and balanced information in this setting (165). Amar-Dolan and colleagues highlighted the importance of a family-centered process for children being discharged with tracheostomies: Important points for families included managing emergencies; navigating home nursing, care coordination, and medical equipment; and setting expectations for home care (166, 167). In a survey of U.S. discharge practices, significant heterogeneity was highlighted among physicians (168), and future work needs to identify contributing factors, data to inform standards, and barriers to implementation to improve overall outcomes.

Pollution and Pediatric Lung Disease

Outdoor Air Pollution

The devastating forest fires that have occurred in the United States, Australia, the Amazon, and other parts of the world have drawn further attention to climate change and its effects on respiratory health. Relatively modest rises in particulate matter ⩽2.5 μm in aerodynamic diameter ($PM_{2.5}$) exposure of 5.6 $\mu g/m^3$ after the San Diego fires in 2017 were associated with pronounced increases in pediatric emergency room respiratory visits (169), and those ZIP codes with the largest increases were all located downwind from fires. This study further supports the importance of health warnings, smoke forecasting, early alert systems, and adequate filtration systems for children with respiratory diseases (170). Mechanisms to inform communities of changes in air quality must also advise activities and exposure accordingly. Using a time-stamped global positioning device with an accelerometer, detrimental effects of traffic-related airway pollution (TRAP) in adolescents were shown to be particularly pronounced when exercising in areas and seasons with higher NO_2 and $PM_{2.5}$ levels (171): Moderate to vigorous outdoor activity was associated with higher NO_2 and, during the warmer months—which have higher outdoor pollution—with poorer lung function.

As highlighted in a 2020 ATS report on outdoor air pollution and new-onset airway disease (172), seminal epidemiological and mechanistic studies have outlined the risk of incident asthma in children exposed to TRAP such as fine particulate matter ($PM_{2.5}$), ozone, NO_2, and black carbon. The potential interaction between this and other environmental factors was highlighted in a case-control study of Puerto Rican children, where living farther away from a major road (as proxy for TRAP) was associated with ∼50% lower odds of asthma, except in children exposed to high levels of dust mite at home (173). Data from ALSPAC (Avon Longitudinal Study of Parents and Children) has reinforced the link between early-life air pollution (in this case, antenatal exposure to TRAP) and lower lung function at 8 years of age (174) in agreement with PARIS and BAMSE birth cohorts (175, 176). Using data on lung function trajectories of 2,000 children from three different cohorts (1993–2001, 1997–2004, and 2007–2011), Urman and colleagues showed that the highest median NO_2 and $PM_{2.5}$ epoch had an FEV_1% growth rate 2.7% lower than expected (177). Thankfully, later epochs recorded not only lower pollution but also improved lung growth. The authors estimated a 30% reduction in NO_2 would have led to 4.4%

increase in FEV_1 growth and a 7.1% increase in FVC growth. The same research group estimated that air quality below 20 ppb NO_2 in California could decrease childhood asthma incidence by 20% (178, 179).

E-Cigarettes and Vaping

The long-term effects of vaping and e-cigarettes are still largely unknown. The different types of devices, solutions, and lexicography used in this fad are broad (180). Although the incidence of e-cigarette or vaping product use–associated lung injury is decreasing, outbreaks remain a major health concern. Recent U.S. Food and Drug Administration regulations only partially address the use of flavoring in vaping fluid in adolescents (181), which is crucial given migration toward sweeter, non–tobacco-based flavors, particularly in younger users (182). Not only did very few users report an intention to stop using e-cigarettes with any U.S. Food and Drug Administration ban, but half reported intention to use "alternative ways" to circumvent it. Sexual identity may be another important factor to consider when identifying at-risk groups: In a survey of over 30,000 youth, the incidence of asthma was higher among youths who both identified as a sexual minority and also reported to be a substance user (183), highlighting the importance of acknowledging and addressing potential stressors within these groups as part of their asthma management.

Conclusions

Recent publications from ATS-sponsored journals as summarized within this update reflect remarkable advances throughout pediatric respiratory and sleep medicine. As with adult pulmonary and critical care medicine, the application of advanced tools and techniques that provide greater functional, structural, and mechanistic insights into lung development, disease evolution, and therapeutic strategies have clearly improved our understanding of the pathobiology and treatment of diverse childhood lung diseases. In addition to addressing such diseases as CF, PCD, developmental lung disorders, asthma, and sleep, we currently face critical challenges in the need to better understand the impact of climate change involving air pollution, vaping, smoking, and the changing environment in which our lungs operate as an especially key focus. Growing recognition of the potential importance of complex host–microbiome interactions are necessary to comprehend its impact on mechanisms of lung disease and its progression, which may lead to novel therapeutic strategies in diverse settings. Finally, exciting advances in lung imaging and applying 'omic technologies to enable accurate and comprehensive phenotyping of pediatric respiratory conditions is another important area in which progress is being made and will be fundamental in our quest for personalized, precise medicine for our patients. ■

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

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