



Pediatric

Year in Review



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Pediatric Year in Review Bibliography

MODERATORS

Paul David Robinson MD, MRCPCH, PhD
The Children’s Hospital at Westmead
Sydney, Australia

Terri A. Laguna, MD, MSci
Ann & Robert H. Lurie Children’s Hospital of Chicago
Chicago, IL

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This session and the International Conference are supported by independent medical educational grants from Genentech, Inc., Vertex Pharmaceuticals, Inc., Boehringer Ingelheim Pharmaceuticals, Inc., GlaxoSmithKline, Merck & Co.

PEDIATRIC PULMONARY VASCULAR DISEASE

Eric D. Austin, MD, MSc

Vanderbilt University Medical Center
Department of Pediatrics
Nashville, TN

DIAGNOSIS AND CLASSIFICATION OF PEDIATRIC PULMONARY HYPERTENSION

Rosenzweig EB, Abman SH, Adata I, Beghetti M, Bonnet D, Haworth S, Dunbar Ivy DD, Berger RMF. **Paediatric pulmonary arterial hypertension: updates on definition, classification, diagnostics and management.** *Eur Respir J.* 2019 Jan 24;53(1):1801916.

Summary

At variable intervals since 1973, international experts have convened a World Symposium on the diagnosis, classification, and management of pulmonary hypertension (PH). Most recently, in 2018, the 6th World Symposium on PH provided several important updates to the diagnosis in children and adults. For over 40 years, PH had been arbitrarily defined as mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg at rest, measured by right heart catheterization. Based upon updated data from normal subjects which showed that normal mPAP was 14.0 ± 3.3 mmHg among those with adult physiology, the definition of PH was revised to require a mPAP > 20 mmHg to be considered for the diagnosis of PH in children and adults. However, because hypertensive pulmonary vascular disease (that is, PH) can be caused by an increase in cardiac output or pulmonary arterial wedge pressure, the 6th WSPH Task Force proposed to include pulmonary vascular resistance ≥ 3 Wood Units in the definition of all forms of pre-capillary PH associated with mPAP > 20 mmHg. Additional changes included updates to the group classification system pulmonary hypertension, including a more pronounced focus upon several unique features of pediatric PH in the setting of hypoxia and/or developmental lung diseases and a broader focus upon the genetic underpinnings of PH in children and adults.

Comments

1. PH is a heterogeneous condition characterized by elevated pulmonary vascular pressures due to a wide variety of causes.
2. The Pediatric Task Force elected to accept the modified the definition for PH of mPAP > 20 mmHg and to include a pulmonary vascular resistance (PVR) ≥ 3 Woods Units to identify pre-capillary PH.
3. The updated classification system for PH was slightly revised but largely unchanged, with 5 major PH subgroups classified.

4. PH due to lung diseases and/or hypoxia (Group 3) was expanded to provide a greater focus upon patients with developmental lung disorders, including major causes of PH in children such as bronchopulmonary dysplasia, congenital diaphragmatic hernia, and Down Syndrome.
5. While risk and benefit must be considered, invasive hemodynamic assessment by cardiac catheterization remains the gold standard for the definitive diagnosis and nature of PAH, performing acute vasoreactivity testing, and providing useful data for risk stratification.

THE GENETIC LANDSCAPE OF PEDIATRIC PULMONARY ARTERIAL HYPERTENSION

Haarman MG, Kerstjens-Frederikse WS, Vissia-Kazemier TR, Breeman KTN, Timens W, Vos YJ, Roofthoof MTR, Hillege HL, Berger RMF. **The Genetic Epidemiology of Pediatric Pulmonary Arterial Hypertension.** *J Peds* 2020 Oct;225:65-73.e5.

Summary

Several studies over the past few years have expanded our understanding of the genetic landscape of pulmonary arterial hypertension (PAH) in children and adults. This manuscript describes a cohort study of 70 children with PAH from the Dutch National registry and explores genotype-phenotype associations and outcomes, building upon recent progress in the field. They described 19 children (27%) with an established PAH-associated gene mutation, as well as 12 children (17%) with other genetic disorders with an established association with PAH. These disorders included Down Syndrome (trisomy 21), Hippel Lindau (VHL) syndrome, and methylmalonic aciduria and homocystinuria type C protein (MMACHC). In another 16 children (23%) they found copy number variations ($n = 13$) or genetic syndromes ($n = 3$) without a known prior established association with PAH. Only 23 of the 70 children with PAH (33%) had no genetic abnormalities identified. Some differences in response to therapy and transplant-free survival were detected between patient groups with different genetic backgrounds, but given the small number more studies are needed to explore genotype-phenotype interactions.

Comments

1. Only 33% of pediatric PAH patients had no detectable genetic variation thought to be responsible for the PH condition, which is much higher than studies of adult patients with PAH.
2. While BMPR2 gene mutations were common, TBX4 gene mutations were the most frequently detected variants.
3. Pulmonary venoocclusive disease (PVOD) was detected in 5 (7%) of PAH patients, 2 of whom had a mutation in the EIF2AK4 gene.
4. Some children with profound genetic abnormalities and associated syndromes may have worse outcomes than other subjects; but, larger studies are needed to explore this issue.
5. Genetic analysis of children with PAH is an important consideration which should be paired with genetic counseling of the parents and as age appropriate, the child.

IMAGING AND OTHER PROCEDURES IN CHILDREN WITH PH

Vaiyani, D, Kelleman M, Downey LA, Usama Kanaan U, Petit J, Bauser-Heaton H. **Risk Factors for Adverse Events in Children with Pulmonary Hypertension Undergoing Cardiac Catheterization.** *Pediatr Cardiol.* 2021 Jan 29. doi: 10.1007/s00246-020-02535-4.

Summary

While cardiac catheterization (CC) is the gold standard for diagnosis of PH, it is not without risk. The invasive nature of CC and associated anesthesia predispose this patient population to adverse events including death and/or need for extracorporeal membrane oxygenation (ECMO). This retrospective study evaluated CC data from procedures conducted between 2011 and 2016 at a single center in North America. The study included 198 CC performed on 191 patients. Adverse events (AEs) were frequent (14.1%), including cardiac arrest, increased respiratory support requiring ICU care, PH crisis, bradycardia/hypotension requiring intervention, and arrhythmias. Odds of an adverse event increased by 22% for every 15-min increase in procedure times and were significantly increased for procedures longer than 80 min. Risk factors for AEs included features of the hemodynamic assessment (higher mPAP) as well as female sex. Younger age, medication regimens, prematurity, and genetic disease did not carry an increased risk. CC for PH is a high risk procedure which should be conducted by specialists and centers comfortable with the diagnosis, management, and procedural care of children with PH.

Comments

1. While CC is the gold standard element necessary to diagnose PH in children and adults, it is not without risk and should be approached judiciously.
2. A wide range of AEs are possible, including more mild such as post-operative site pain as well as more severe events including acute cardiopulmonary decline requiring ICU-level care, cardiac arrest, and death.

3. Risk factors for AEs include not only the a priori severity of the clinical condition, but also female sex as well as elevated mPAP during the procedure.
4. The timing and approach to CC in children with PH, or suspected PH, is often necessary. However, specialists comfortable with the care of children with PH, and its related procedural approaches, are recommended when possible.

BIOLOGIC MARKERS OF PEDIATRIC PH DIAGNOSIS AND SEVERITY

Griffiths M, Yang J, Simpson CE, Vaidya D, Nies M, Brandal S, Damico R, Ivy D, Austin ED, Pauciulo MW, Lutz KA, Rosenzweig EB, Hirsch R, Yung D, Nichols WC, Everett AD. **ST2 is a biomarker of pediatric pulmonary arterial hypertension severity and clinical worsening.** *CHEST* 2021 Feb 17;S0012-3692(21)00284-1.

Summary

Noninvasive diagnostic and prognostic markers of pediatric pulmonary hypertension (PH) that are more pulmonary vascular specific have been elusive due to disease heterogeneity and patient growth. For example, while a helpful tool, BNP and NT-proBNP are cardiac-derived and difficult to interpret in pediatrics due to effects from age, sex, congenital-heart disease, a general lack of age-specific normal values, and other concerns. Furthermore, clinical risk assessment approaches are lacking in the pediatric PH field. This study sought to assess whether ST2, a member of the Interleukin-1 receptor family, is produced by the pulmonary endothelium and could be used as prognostic marker of hemodynamic worsening and adverse outcomes in pediatric PH. Indeed, in two large patient cohorts, ST2 was associated with worse hemodynamics and shorter time to deleterious events. In addition, adding the ST2 level to prior risk score algorithm (REVEAL-risk score) improved prediction of adverse outcomes.

Comments

1. Prognostic algorithms to support clinical-decision making are an area of intense interest in the PH field, but particularly lacking pediatric-specific advances.
2. Two prior smaller studies found that ST2 associated with indices of disease severity in pediatric PH, providing background support of this study which used two large cohorts.
3. ST2 is produced and secreted by the pulmonary artery endothelial cells, making it potentially complementary to BNP/NT-proBNP, which are cardiac-derived.
4. ST2 associated with several key hemodynamic findings of pulmonary arterial hypertension (increased mPAP, PVR, PVRi), with the long-term functional decline associated with the disease, and ultimately mortality or need for transplant/palliative shunt.
5. Addition of ST2 to the REVEAL risk score algorithm enhanced the prediction of adverse outcomes.

TREATMENT OF PEDIATRIC PH

Haarman MG, Lévy M, Roofthoof MTR, Douwes JM, Vissia-Kazemier TR, Szezepanski I, Berger RMF, Bonnet D. **Upfront triple combination therapy in severe paediatric pulmonary arterial hypertension.** *Eur Respir J* 2021; 57: 2001120; DOI: 10.1183/13993003.01120-2020.

Summary

Treatment strategies for pediatric pulmonary arterial hypertension (PAH) have evolved over the last years, but survival remains poor. Upfront triple combination therapy (uTCT) at the time of diagnosis has been reported to show significant clinical improvement and excellent long-term outcome recently in adults; but, the relevance to pediatric PAH is unclear. The investigators retrospectively analyzed existing data on uTCT from the French and Dutch pediatric PH centres. They found that children with severe PAH treated with uTCT benefitted well, with sustained status up to 1 year in the majority of children. Transplant-free survival rates at 1-, 2- and 3-years were superior to predicted transplant-free survival estimates calculated using the existing prediction tools. However, almost half of the children received a Potts (or modified Potts) shunt during follow-up, demonstrating that despite benefit from uTCT, disease progression continued.

Comments

1. Current guidelines for the treatment of PAH recommend the start of combination therapy instead of monotherapy in patients at high risk, with recent studies in adults suggesting enhanced benefit with uTCT using sildenafil or similar class agent, bosentan or similar class agent, and prostacyclin or a similar class agent.
2. This was a small retrospective study, of only 21 children, but did show benefit from uTCT.
3. Invasive haemodynamics, assessed in half of the children, showed a 50% reduction in PVRi, 30% reduction of mPAP and 20% increase in cardiac index, all suggestive of hemodynamic response.
4. However, nearly half of the children underwent a Potts (or modified Potts) shunt, demonstrating a need for additional intervention, mainly due to clinical worsening or lack of improvement.
5. Optimal risk prediction tools for children with PAH are also lacking and will be an important component of therapeutic decision-making studies such as these which need to be conducted prospectively.
6. This study, and similar studies of pediatric PH treatment, focus upon Group 1 PH (PAH); studies of other PH subtypes are of substantial need.

OTHER ARTICLES OF INTEREST

The Genetic Landscape of Pediatric Pulmonary Arterial Hypertension

(Review) Welch CL, Chung WK. **Genetics and Other Omics in Pediatric Pulmonary Arterial Hypertension.** *Chest*. 2020 May;157(5):1287-1295. doi: 10.1016/j.chest.2020.01.013.

Gelinas SM, Benson CE, Khan MA, Berger RMF, Trembath RC, Machado RD, Southgate L. **Whole Exome Sequence Analysis Provides Novel Insights into the Genetic Framework of Childhood-Onset Pulmonary Arterial Hypertension.** *Genes (Basel)*. 2020 Nov 11;11(11):1328.

Imaging and Other Procedures in Children with PH

Hocq C, Vanhoutte L, Guilloteau A, Massolo AC, Van Grambezen B, Carkeek K, Piersigilli F, Danhaive O; from the European Society for Pediatric Research. **Early diagnosis and targeted approaches to pulmonary vascular disease in bronchopulmonary dysplasia.** *Pediatr Res*. 2021 Mar 5.

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(Review) Levy PT, Jain A, Nawaytou H, Teitel D, Keller R, Fineman J, Steinhorn R, Abman SH, McNamara PJ; Pediatric Pulmonary Hypertension Network (PPHNet). **Risk Assessment and Monitoring of Chronic Pulmonary Hypertension in Premature Infants.** *J Pediatr*. 2020 Feb;217:199-209.e4.

Biologic Markers of Pediatric PH Diagnosis and Severity

Said F, Haarman MG, Roofthoof MTR, Hillege HL, Ploegstra MJ, Berger RMF. **Serial Measurements of N-Terminal Pro-B-Type Natriuretic Peptide Serum Level for Monitoring Pulmonary Arterial Hypertension in Children.** *J Pediatr*. 2020 May;220:139-145.

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Treatment of Pediatric PH

Ivy DD, Beghetti M, Juaneda-Simian E, Miller D, Lukas MA, Ioannou C, Okour M, Jun Narita, Berger, RMF. **A Randomized Study of Safety and Efficacy of Two Doses of Ambrisentan to Treat Pulmonary Arterial Hypertension in Pediatric Patients Aged 8 Years up to 18 Years.** *The Journal of Pediatrics: X, Volume 5, 2020.*

Schweintzger S, Koestenberger M, Schlagenhaut A, Grangl G, Burmas A, Kurath-Koller S, Pocivalnik M, Sallmon H, Baumgartner D, Hansmann G, Gamillscheg A. **Safety and efficacy of the endothelin receptor antagonist macitentan in pediatric pulmonary hypertension.** *Cardiovasc Diagn Ther.* 2020 Oct;10(5):1675-1685.

Aypar E, Alehan D, Karagöz T, Aykan H, Ertugrul İ. **Clinical efficacy and safety of switch from bosentan to macitentan in children and young adults with pulmonary arterial hypertension: extended study results.** *Cardiol Young.* 2020 May;30(5):681-685.

Hansmann G, Meinel K, Bukova M, Chouvarine P, Wählander H, Koestenberger M; European Pediatric Pulmonary Vascular Disease Network (EPPVDN). **Selexipag for the treatment of children with pulmonary arterial hypertension: First multicenter experience in drug safety and efficacy.** *J Heart Lung Transplant.* 2020 Jul;39(7):695-706.

CHILDHOOD INTERSTITIAL LUNG DISEASE (chILD)

Jennifer Wambach, MD, MS

Washington University School of Medicine
Department of Pediatrics
St. Louis, MO

GENE THERAPY TO TREAT SURFACTANT PROTEIN B DEFICIENCY IN A MURINE MODEL

Kang MH, van Lieshout LP, Xu L, Domm JM, Vadivel A, Renesme L, Muhfeld C, Hurskainen M, Mizikova I, Pei Y, van Vloten JP, Thomas SP, Milazzo C, Cyr-Depauw C, Whitsett JA, Nogee LM, Wootton SK, Thebaud B. **A lung tropic AAV vector improves survival in a mouse model of surfactant B deficiency.** *Nat Commun.* 2020 Aug 6;11(1):3929.

Summary

Surfactant protein-B (SP-B) is synthesized by alveolar type 2 cells and required for surfactant function. SP-B deficiency is a monogenic, autosomal recessive disorder that results in severe neonatal respiratory distress syndrome that is lethal without lung transplantation. SP-B deficient mice die shortly after birth from respiratory failure. The authors used an adeno-associated virus 6 (AAV6.2FF) capsid that efficiently transduces lung epithelial cells to intratracheally administer murine or human proSFTPB cDNA into SP-B deficient mice. The vector resulted in restoration of surfactant homeostasis, prevention of lung injury, improved lung physiology, and prolonged median survival beyond 200 days. The vector also transduced human lung tissue, demonstrating its potential for clinical application for infants with SP-B deficiency.

Comments

1. Targeted gene therapy to the alveolar surface of AT2 cells is a promising approach for correction of lethal monogenic lung diseases including SP-B deficiency.
2. The response to AAV6.2FF gene therapy was dose dependent with the highest doses having the greatest effect on survival, suggesting clinical application may require repeated dosing or be a bridge to more definitive therapy of lung transplant.
3. Prior obstacles of adenoviral gene therapy including cell-surface receptors required for entry and ubiquitin-mediated degradation were overcome with targeted engineering of the AAV capsid.
4. While cells other than AT2 cells of the distal lung and airways were transduced by AAV6.2FF gene therapy, transduction was non-toxic and did not illicit an inflammatory cytokine response.
5. AAV6.2FF gene therapy may provide a therapeutic platform for other monogenic lung diseases that affect AT2 cells including ABCA3 deficiency or SP-C dominant negative mutations.

NANOPARTICLE DELIVERY OF STAT3 TO TREAT ACDMPV IN A MURINE MODEL

Pradhan A, Dunn A, Ustiyani V, Bolte C, Wang G, Whitsett JA, Zhang Y, Porollo A, Hu YC, Xiao R, Szafranski P, Shi D, Stankiewicz P, Kalin TV, Kalinichenko VV. **The S52F FOXF1 Mutation Inhibits STAT3 Signaling and Causes Alveolar Capillary Dysplasia.** *Am J Respir Crit Care Med.* 2019 Oct 15;200(8):1045-1056.

Summary

FOXF1 is a critical transcription factor that regulates embryonic lung development. Mutations or deletions of the FOXF1 gene locus are associated with alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV), however, the mechanism underlying this association is not well characterized. ACDMPV presents as refractory pulmonary hypertension and severe respiratory failure in neonates and is lethal without lung transplantation. The authors used CRISPR/Cas9 genome editing to introduce a heterozygous, pathogenic Foxf1 missense mutation (S52F) into mice. The knock-in mice (WT/S52F) recapitulated many of the histopathologic findings of ACDMPV infants, establishing a clinically relevant murine model of ACDMPV. The S52F FOXF1 mutant protein disrupted STAT3–FOXF1 protein–protein interactions, inhibited transcription of Stat3, a critical transcriptional regulator of angiogenesis, did not bind chromatin, and was transcriptionally inactive. The authors developed a highly efficient nanoparticle formulation to intravenously deliver STAT3 cDNA which restored endothelial proliferation and stimulated lung angiogenesis in Foxf1 WT/S52F mice.

Comments

1. WT/S52F mice recapitulate many of the histopathologic findings of ACDMPV infants, establishing a clinically relevant murine model of ACDMPV.
2. FOXF1 acts through STAT3 to stimulate neonatal lung angiogenesis.
3. Intravenous nanoparticle delivery of STAT3 increased vascularity and improved lung structure in WT/S52F mice with ACDMPV.
4. STAT3 may have clinical application for infants with ACDMPV due to FOXF1 mutations that reduce STAT3 activity; however, as gain-of-function mutations in STAT3 cause an autoimmune disease that can affect the lungs, therapeutic application must be carefully investigated.

5. While not all pathogenic mutations in FOXF1 disrupt STAT3-FOXF1 interaction, this model suggests a potential therapy for this lethal disorder.

PULMONARY APTAMER SIGNATURES AS BIOMARKERS FOR CHILD

Deterding RR, Wagner BD, Harris JK, DeBoer EM.

Pulmonary Aptamer Signatures in Children's Interstitial and Diffuse Lung Disease. *Am J Respir Crit Care Med.* 2019 Dec 15;200(12):1496-1504.

Summary

Biomarkers are needed in chILD to improve diagnosis, monitor disease progression, determine disease pathogenesis, and develop new therapies. Using SOMAmer (Slow Off-rate Modified Aptamer), a proteomic assay that uses nucleic acid-based protein-binding reagents to identify over 1000 proteins, the authors analyzed banked bronchoalveolar lavage fluid (BALF) samples collected from children with neuroendocrine cell hyperplasia of infancy (NEHI), surfactant dysfunction mutations (ABCA3 and SFTPC), and controls. Protein levels were compared between groups and classified into pathways; hierarchical clustering was used to define endotypes. Children with NEHI and surfactant mutations had distinct proteomic profiles that differed from controls. Proteins associated with inflammation and pulmonary fibrosis were enriched in the samples from surfactant dysfunction group, but not the NEHI group. Hierarchical clustering identified 2 NEHI endotypes, which did not correlate with identified clinical factors and may result from underlying genetic or environmental mechanisms. Proteomic profiles can be used to distinguish between chILD disorders and may improve diagnosis and monitoring of disease progression.

Comments

1. Proteomic biomarkers may improve diagnosis and monitoring of disease progression for chILD disorders.
2. Proteomic assays performed on bronchoalveolar lavage fluid samples distinguish between NEHI and surfactant dysfunction mutations.
3. Proteomic profiles from children with ABCA3 and SFTPC mutations similarly identified inflammatory and fibrotic proteins and support grouping these disorders for therapeutic approach.
4. Two NEHI endotypes were identified with proteomic assay that did not correlate with identified clinical factors and may result from underlying genetic or environmental mechanisms.
5. Proteomic biomarkers may inform novel chILD disease mechanisms and target potential therapeutic strategies.

HIGH MORTALITY LUNG DISEASE AMONG CHILDREN WITH SYSTEMIC JUVENILE ARTHRITIS

Saper VE, Chen G, Deutsch GH, Guillerman RP, Birgmeier J, Jagadeesh K, Canna S, Schulert G, Deterding R, Xu J, Leung AN, Bouzoubaa L, Abulaban K, Baszis K, Behrens EM, Birmingham J, Casey A, Cidon M, Cron RQ, De A, De Benedetti F, Ferguson I, Fishman MP, Goodman SI, Graham TB, Grom AA, Haines K, Hazen M, Henderson LA, Ho A, Ibarra M, Inman CJ, Jerath R, Khawaja K, Kingsbury DJ, Klein-Gitelman M, Lai K, Lapidus S, Lin C, Lin J, Liptzin DR, Milojevic D, Mombourquette J, Onel K, Ozen S, Perez M, Phillipi K, Prahalad S, Radhakrishna S, Reinhardt A, Riskalla M, Rosenwasser N, Roth J, Schneider R, Schonenberg-Meinema D, Shenoi S, Smith JA, Sönmez HE, Stoll ML, Towe C, Vargas SO, Vehe RK, Young LR, Yang J, Desai T, Balise R, Lu Y, Tian L, Bejerano G, Davis MM, Khatri P, Mellins ED. **Emergent high fatality lung disease in systemic juvenile arthritis.** *Ann Rheum Dis.* 2019 Dec;78(12):1722-1731.

Summary

Systemic juvenile idiopathic arthritis (sJIA) is a chronic inflammatory disease characterized by arthritis and systemic inflammation. Increasingly, parenchymal lung disease has been identified in patients with sJIA. In this multicenter, retrospective study, the authors identified the clinical, radiologic, and histologic characteristics associated with parenchymal lung disease among 61 children with sJIA. Development of lung disease was associated with acute erythematous clubbing, pruritic and non-evanescent rashes, peripheral eosinophilia, elevated serum ferritin, lymphopenia, younger age of sJIA onset, exposure to IL-1 or IL-6 inhibitors, and history of anaphylaxis to IL-6 inhibitor tocilizumab. Chest CT patterns included septal thickening involving the periphery of multiple lobes with or without ground-glass opacities. The predominant histopathologic findings were pulmonary alveolar proteinosis (PAP) and endogenous lipid pneumonia (ELP). The 5-year survival for children with sJIA and parenchymal lung disease was 42%. While a consistent monogenic etiology was not identified, trisomy 21 was associated with increased risk for parenchymal lung disease. High mortality parenchymal lung disease occurs in patients with sJIA, is associated with prior exposure to cytokine inhibitors, and may be related to macrophage dysfunction.

Comments

1. Pulmonary manifestations may occur with pediatric rheumatologic disorders and may be associated with significant morbidity and mortality.
2. Children with sJIA are at risk for developing high mortality parenchymal lung disease and should be carefully monitored for respiratory symptoms.

3. Development of parenchymal lung disease in patients with sJIA is associated with prior exposure to cytokine inhibitors.
 4. Histopathology demonstrates pulmonary alveolar proteinosis and endogenous lipoid pneumonia, suggesting macrophage dysfunction.
 5. Investigation of the disease mechanisms underlying parenchymal lung disease in sJIA and treatment/prevention strategies are urgently needed.
2. chILD disorders are individually rare and heterogeneous, and thus require innovative, carefully designed, multicenter clinical trials to study potential therapies.
 3. As data regarding the natural history of fibrosing chILD is limited, the placebo group may provide important information regarding lung function and baseline adverse events.
 4. This international clinical trial represents a major advance for the field of chILD and will inform future interventional trials for rare pediatric diseases.

NINTEDANIB CLINICAL TRIAL FOR FIBROSING CHILD

Deterding R, Griese M, Deutsch G, Warburton D, DeBoer EM, Cunningham S, Clement A, Schwerk N, Flaherty KR, Brown KK, Voss F, Schmid U, Schlenker-Herceg R, Verri D, Dumistracel M, Schiwiek M, Stowasser S, Tetzlaff K, Clerisme-Beaty E, Young LR. **Study design of a randomized, placebo controlled trial of nintedanib in children and adolescents with fibrosing interstitial lung disease.** *ERJ OpenRes* 2021; *In press*.

Summary

More than 200 rare, heterogeneous respiratory disorders are classified as chILD with no currently approved therapies and variable prognoses. Among adults with progressive fibrosis due to ILD, nintedanib reduces the rate of forced vital capacity (FVC) decline. The authors present a multicenter, prospective, randomized, double-blind, placebo-controlled clinical trial of nintedanib for pediatric patients with fibrosing chILD. Inclusion criteria are children aged 6–17 years with clinically significant fibrosing ILD as noted on high resolution computed tomography, FVC $\geq 25\%$ predicted, and clinically significant disease (Fan score of ≥ 3 or evidence of clinical progression over time) with a minimum target of 30 patients (goal of >20 adolescents aged 12–17 years). Exclusion criteria are underlying chronic liver disease, significant pulmonary arterial hypertension, cardiovascular disease, or increased bleeding risk. Patients will be randomized 2:1 to receive oral nintedanib or placebo for 24 weeks on top of standard care with starting doses based on patient weight using allometric scaling. After 24 weeks, all patients will receive open-label nintedanib until the end of study (52 weeks) or discontinuation. The primary endpoints are pharmacokinetics and safety. Secondary endpoints will be assessed at weeks 24 and 52 and include change in FVC% predicted from baseline, somatic growth, dental abnormalities, Pediatric Quality of Life Questionnaire™, oxygen saturation, and 6-minute walk distance. This international collaboration is the first randomized controlled trial of an antifibrotic agent for chILD and represents a major advance for the field.

Comments

1. There are no currently approved therapies for chILD, and treatment options are limited and based on anecdotal evidence (e.g., steroids, hydroxychloroquine, azithromycin).

OTHER ARTICLES OF INTEREST

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CYSTIC FIBROSIS

Jessica E. Pittman, MD, MPH

Washington University School of Medicine
Department of Pediatrics
Saint Louis, MO

DIAGNOSING CF: MANAGEMENT AND DIAGNOSIS OF CRMS/CFSPID

Barben J, Castellani A, Munck A, Davies JC, de Winter-deGroot KM, Gartner S, Kashirskaya N, Linnane B, Mayell SJ, McColley S, Ooi CY, Proesmans M, Ren CL, Salinas DS, Sermet-Gaudelus I, Sommerburg O, Southern KW. **Updated guidance on the management of children with cystic fibrosis transmembrane conductance regulator-related metabolic syndrome/ cystic fibrosis screen positive, inconclusive diagnosis (CRMS/CFSPID)**. *Journal of Cystic Fibrosis*. <https://doi.org/10.1016/j.jcf.2020.11.006>.

Summary

Inclusion of CF in newborn screening (NBS) algorithms has facilitated earlier diagnosis/intervention for patients, but has led to a population of young children with inconclusive diagnosis now referred to as CRMS/CFSPID, reflecting the initial U.S. (CFTR-related metabolic syndrome) and international (CF screen positive, inconclusive diagnosis) terminologies. CRMS/CFSPID is now defined as being present in an asymptomatic child with positive NBS and either a) normal sweat chloride and two identified CFTR variants (at least one of unclear significance) or b) intermediate sweat chloride and 0-2 identified CFTR variants, with less than two of known significance. There has been marked variability in the management of these patients; the authors attempt to provide consensus recommendations for classification and management, and to summarize current understanding of the likelihood of these patients to develop significant CF disease, or to convert to a diagnosis of CF. Recommendations include harmonized terminology (CRMS/CFSPID), clear discussions with families about potential for change in diagnosis in the future, and annual evaluations in childhood with an extensive evaluation at 6 years of age to more formally define any lung disease and determine the need for further follow up with a CF specialist.

Comments

1. Harmonization of terminology for CRMS/CFSPID is necessary to better define and classify these patients, avoid caregiver/provider confusion, prevent inappropriate assignment of diagnosis of CF, and emphasize lack of symptoms related to CF disease.
2. Variability in newborn screening protocols has a significant impact on ratios of CF vs. CRMS/CFSPID, which subsequently

influences reported rates of conversion from CRMS/CFSPID to CF, as programs with higher rates of diagnosis of CRMS/CFSPID saw lower rates of conversion to CF. CFF Patient Registry data showed an 11% conversion rate, while other reports range from 5 – 45%.

3. The majority CRMS/CFSPID diagnoses subsequently converted to a CF diagnosis were based on elevation in repeat sweat chloride testing or change in designation of CFTR variant, as opposed to a change in clinical picture. As the authors point out, “these children always had CF,” but remained asymptomatic or with only mild clinical manifestations.
4. The majority of children with CRMS/CFSPID remain asymptomatic in early childhood; even if their diagnosis is subsequently converted to CF, they remain difficult to distinguish epidemiologically from other children with CRMS/CFSPID.
5. Authors suggest a minimum of annual evaluations for young children with CRMS/CFSPID, with a more extensive evaluation at 6 years of age as a decision point to cement diagnosis and determine need for follow up.

LUNG FUNCTION TESTING IN CF: MBW VS. SPIROMETRY

Perrem L, Stanojevic S, Shaw M, Jensen R, McDonald N, Isaac SM, Davis M, Clem C, Guido J, Jara S, France L, Solomon M, Grasemann H, Waters V, Sweezey N, Sanders DB, Davis SD, Ratjen F. **Lung Clearance Index to Track Acute Respiratory Events in School-age Children with Cystic Fibrosis**. *Am J Respir Crit Care Med*. 2020 Oct 8. doi: 10.1164/rccm.202006-2433OC. Epub ahead of print. PMID: 33030967.

Summary

School-aged children with CF were followed longitudinally for two years in a multicenter, prospective observational study, with Nitrogen multiple breath washout (MBW) testing and spirometry performed quarterly and during acute respiratory events. Primary outcome measures included the lung clearance index (LCI) measured by MBW and FEV1 measured by spirometry. Correlations between LCI and FEV1, change in each measure at the time of respiratory event, and recovery to baseline lung function at follow up from a respiratory event were assessed. Ninety-eight children experienced a total of 265 acute respiratory events (the majority with mild symptoms), defined as a pulmonary exacerbation if treated with antibiotics or “increased cough event” if

untreated. Both LCI and FEV1 were noted to worsen (>10% change) with acute respiratory events, with 54% of events associated with worsening of either measure. LCI was more likely to worsen than with respiratory events than FEV1 (42% vs. 30%); most notably, worsened LCI was associated with both exacerbations and increased cough events (though change was less pronounced), while FEV1 did not significantly worsen with increased cough events. A small, but important, proportion of subjects did not return to >90% of baseline following exacerbation – 25% for LCI and 14% for FEV1.

Comments

1. LCI appeared more sensitive to acute changes in lung function than FEV1, particularly those associated with mild events not treated with antibiotics.
2. Abnormalities in LCI and FEV1 were discordant, suggesting the potential utility of these measures in combination to monitor changes in lung function in patients with mild CF lung disease.
3. A small, but important, percentage of subjects did not return to >90% of their baseline FEV1 or LCI, highlighting the need for aggressive monitoring and treatment even in young children with mild CF lung disease.
4. Association of worsening of LCI with events perceived as more mild, and without significant change in FEV1, highlights the potential of MBW testing for improving diagnosis of pulmonary exacerbations and guiding therapeutic interventions.

NUTRITION IN CF: IMPACT OF GI MICROBIOTA

Hayden HS, Eng A, Pope CE, Brittnacher M J, Vo AT, Weiss EJ, Hager KR, Martin BD, Leung DH, Heltshe SL, Borenstein E, Miller SI, Hoffman LR. **Fecal dysbiosis in infants with cystic fibrosis is associated with early linear growth failure.** *Nat Med* 26, 215–221 (2020). <https://doi.org/10.1038/s41591-019-0714-x>.

Summary

While NBS has led to improvements in weight gain in infants with CF, many still demonstrate poor linear growth in the first year of life. Abnormalities in the CF GI tract, including inflammation, impaired transit, abnormal mucus, and alterations in pH, may impact the GI microbiome, which plays roles in growth regulation including nutrient absorption and production of metabolites that regulate metabolism and growth hormones. This study investigated association of GI microbiota and linear growth by comparing fecal samples from children with CF (N=207) with normal vs. low length as well as healthy controls (N = 25) at 4, 6, and 12 months of age. Children with CF were noted to have taxonomic differences in fecal microbiota compared to controls by 4 months, with higher abundance of Proteobacteria and lower Bacteroidetes. Low-length infants had more extreme dysbiosis, again with higher relative abundance of Proteobacteria and

lower abundance of Bacteroidetes compared to their counterparts with normal length. Findings were significant independent of diet or antibiotic use, and were present despite adequate weight gain.

Comments

1. Infants with CF appear to have “delayed maturation” of fecal microbiota relative to health controls.
2. Delayed maturation is more pronounced in infants with CF and low length, and is significantly different when compared to children with CF and normal length.
3. The authors suggest that decreased synthesis and degradation of short-chain fatty acids due to this delayed maturation (and resulting deficiencies in specific taxa within the fecal microbiota) may play a role in poor linear growth in children with CF.
4. Fat malabsorption may play an important role in delayed maturation of fecal microbiota, and thus have both a direct and indirect impact on linear growth in children with CF.

CF THERAPIES: ELX/TEZ/IVA IN CHILDREN 6 THROUGH 11 YEARS OF AGE

Zemanick ET, Taylor-Cousar JL, Davies J, Gibson RL, Mall MA, McKone EF, McNally P, Ramsey BW, Rayment JH, Rowe SM, Tullis E, Ahluwalia N, Chu C, Ho T, Moskowitz SM, Noel S, Tian S, Waltz D, Weinstock TG, Xuan F, Wainwright CE, McColley SA; VX18-445-106 Study Group. **A Phase 3 Open-Label Study of ELX/TEZ/IVA in Children 6 Through 11 Years of Age With CF and at Least One F508del Allele.** *Am J Respir Crit Care Med.* 2021 Mar 18. doi: 10.1164/rccm.202102-0509OC. Epub ahead of print. PMID: 33734030.

Summary

CFTR modulator elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) has been shown to be remarkably effective in patients with CF 12 years of age and older. The authors present results of a 24 week Phase 3 open-label study of ELX/TEZ/IVA in children with CF 6 to 11 years of age with at least one F508del CFTR allele. Children <30 kg received 50% of the adult daily dose, while those 30 kg and over received full adult dosing. Primary endpoints were safety and tolerability. Sixty-six children were enrolled, nearly evenly split between F508del homozygotes and minimal function heterozygotes. All but one child experienced an AE, the majority of which were mild (55%) or moderate (42%); including headache, cough, and pyrexia. Elevations of aminotransferases greater than three times the ULN occurred in 11% of subjects, none of which necessitated study drug interruption/discontinuation. Sixteen children (24%) experienced rash; one discontinued study drug. A mean absolute change in FEV1 percent predicted from baseline of 10.2 percentage points was seen as early as two weeks after drug initiation and persisted through study termination. Lung clearance index values, CFQ-R

respiratory domain scores, sweat chloride values, BMI and BMI weight-for-age z-score, weight and weight-for-age z-score all improved throughout the treatment period.

Comments

1. Treatment with ELX/TEZ/IVA was well tolerated in children 6 to 11 years of age with CF and at least one F508del CFTR allele; safety profile appeared similar to that of the drug in older patients.
2. Elevation of aminotransferases was seen in 11% of subjects, while rash was reported in 24%; the majority did not require drug discontinuation or interruption.
3. Despite the higher baseline lung function (FEV1 mean 88.8% predicted) in these younger children, a clinically and statistically significant improvement in FEV1 was noted early in the course of treatment, and sustained throughout the study, lending weight to arguments for early introduction of modulator therapies as we move towards primary prevention of CF lung disease.
4. Improvements in nutritional measures (BMI, weight) with ELX/TEZ/IVA may also have long-term impacts on patient health if sustained with clinical use.

THERAPEUTIC TARGETS: CFTR EXPRESSION IN AIRWAY EPITHELIA

Okuda K, Dang H, Kobayashi Y, Carraro G, Nakano S, Chen G, Kato T, Asakura T, Gilmore RC, Morton LC, Lee RE, Mascenik T, Yin WN, Barbosa Cardenas SM, O'Neal YK, Minnick CE, Chua M, Quinney NL, Gentzsch M, Anderson CW, Ghio A, Matsui H, Nagase T, Ostrowski LE, Grubb BR, Olsen JC, Randell SH, Stripp BR, Tata PR, O'Neal WK, Boucher RC. **Secretory Cells Dominate Airway CFTR Expression and Function in Human Airway Superficial Epithelia.** *Am J Respir Crit Care Med.* 2020 Dec 15. doi: 10.1164/rccm.202008-3198OC. Epub ahead of print. PMID: 33321047.

Summary

A precise understanding of CFTR expression and function in the airway epithelia is necessary to identify cellular targets for potential molecular therapeutic interventions. This study employed single-cell RNAseq (scRNA-seq), single cell-based quantitative RT-PCR (scqRT-PCR), and single cell-based RNA in situ hybridization (scRNA-ISH) to determine CFTR expression by cell type in normal human airway epithelia as well as CF lungs. Secretory cells were the most common CFTR+ cells, followed by basal, then ciliated, then ionocytes. Of note, scRNA-seq markedly underestimated the prevalence of CFTR+ cells compared with scRNA-ISH and scqRT-PCR, with a greater than 10 fold underestimation of secretory cell prevalence, in particular. Ionocytes were noted to have the highest level of CFTR expression per cell, without major differences between the three other cell types. Combining cell number/prevalence and CFTR expression, secretory cells

were the dominant expressors of CFTR in human airway epithelia, followed by basal cells. Though ionocytes had the highest CFTR levels per cell, they ranked third due to relative scarcity. Distribution of CFTR expression was similar in CF lungs, again dominated by secretory cells. The authors also demonstrated CFTR-mediated Chloride secretion in CF airway secretory cells after lentiviral transduction of wild-type CFTR.

Comments

1. Secretory cells appear to be the dominant CFTR expressor in superficial airway epithelia in both healthy and CF lungs, and may be an important future therapeutic target.
2. Secretory cells appear to play a dominant role in airway ion transport and Cl⁻ secretion, and thus may have a significant impact on mucus and airway surface hydration.
3. Targeting basal cells or secretory cells with introduction of wild-type CFTR may subsequently impact the other cell line, as basal cells may move into a secretory cell lineage and secretory cells may enter a proliferative basal cell population.
4. These data would suggest that ionocytes are a less viable target for therapeutic interventions in CF lung disease.

OTHER ARTICLES OF INTEREST

MODULATOR THERAPIES

Guimbellot JS, Baines A, Paynter A. et al., **Long term clinical effectiveness of ivacaftor in people with theG551D CFTR mutation,** *Journal of Cystic Fibrosis,* <https://doi.org/10.1016/j.jcf.2020.11.008>

Flume PA, Biner RF, Downey DG, et al. **Long-term safety and efficacy of tezacaftor-ivacaftor in individuals with cystic fibrosis aged 12 years or older who are homozygous or heterozygous for Phe508del CFTR (EXTEND): an open-label extension study.** *The Lancet. Respiratory Medicine.* 2021 Feb. DOI: 10.1016/s2213-2600(20)30510-5.

Chilvers MA, Davies JC, Milla C, Tian S, Han Z, Cornell AG, Owen CA, Ratjen F. **Long-term safety and efficacy of lumacaftor-ivacaftor therapy in children aged 6-11 years with cystic fibrosis homozygous for the F508del-CFTR mutation: a phase 3, open-label, extension study.** *Lancet Respir Med.* 2021 Jan 28:S2213-2600(20)30517-8. doi: 10.1016/S2213-2600(20)30517-8. Epub ahead of print. Erratum in: *Lancet Respir Med.* 2021 Feb 16;: PMID: 33516285.

ANTIBIOTIC TREATMENT REGIMENS

Hewer SCL, Smyth AR, Brown M, Jones AP, Hickey H, Kenna D, Ashby D, Thompson A, Williamson PR; TORPEDO-CF study group. **Intravenous versus oral antibiotics for eradication of Pseudomonas aeruginosa in cystic fibrosis (TORPEDO-CF): a randomised controlled trial.** *Lancet Respir Med.* 2020 Oct;8(10):975-

986. doi: 10.1016/S2213-2600(20)30331-3. PMID: 33007285; PMCID: PMC7606906.

Cogen JD, Faino AV, Onchiri F, Gibson RL, Hoffman LR, Kronman MP, Rosenfeld M, Nichols DP. **Effect of Concomitant Azithromycin and Tobramycin Use on Cystic Fibrosis Pulmonary Exacerbation Treatment.** *Ann Am Thorac Soc.* 2021 Feb;18(2):266-272. doi: 10.1513/AnnalsATS.202002-176OC. PMID: 32810412; PMCID: PMC7869777.

STRUCTURAL AND FUNCTIONAL LUNG DISEASE

Sandvik RM, Kongstad T, Green K, Voldby C, Buchvald F, Skov M, Pressler T, Nielsen KG. **Prospective longitudinal association between repeated multiple breath washout measurements and computed tomography scores in children with cystic fibrosis.** *J Cyst Fibros.* 2020 Oct 4:2121. doi: 10.1016/j.jcf.2020.09.010. Epub ahead of print. PMID: 33028501.

Wilmering MM, Roach DJ, Kramer EL, Walkup LL, Cleveland ZI, Woods JC. **Sensitive structural and functional measurements and 1-year pulmonary outcomes in pediatric cystic fibrosis,** *Journal of Cystic Fibrosis*, 2020, ISSN 1569-1993, <https://doi.org/10.1016/j.jcf.2020.11.019>.



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