ATS 2019 – DALLAS

Pediatric Year in Review Bibliography

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This session and the International Conference are supported by educational grants from Insmed Incorporated, Vertex Pharmaceuticals, Inc. All CME sessions have been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) and are free of the control of commercial interests.
NEXT GENERATION CYSTIC FIBROSIS CONDUCTANCE REGULATOR (CFTR) COMBINATION THERAPY


Summary
The study evaluates the effects of triple combination therapy, VX659-tezacaftor-ivacaftor, on PheF508del CFTR function in subjects who were either homozygous for the mutation or heterozygous for Phe508del with a minimal function CFTR mutation. In this randomized controlled double-blind multicenter trial there was a marked improvement in FEV1, reduction in the sweat chloride concentrations and improvement in the CFQR when subjects received triple therapy.

Comments
1. There was a > 9% improvement in FEV1 when on triple therapy.
2. The safety and side effect profiles were acceptable.
3. Sweat chloride concentrations decreased significantly while on triple therapy.


Summary
The study evaluates the effects of triple combination therapy, VX451-tezacaftor-ivacaftor, on PheF508del CFTR function in subjects who were either homozygous for the mutation or heterozygous for Phe508del with a minimal function CFTR mutation. In this randomized controlled double-blind multicenter trial there was a marked improvement in FEV1, reduction in the sweat chloride concentrations and improvement in the CFQR when subjects received triple therapy.

Comments
1. There was a > 10% improvement in FEV1 when on triple therapy.
2. The safety and side effect profiles were acceptable.
3. Sweat chloride concentrations decreased significantly while on triple therapy.

THE USE OF CYSTIC FIBROSIS CONDUCTANCE REGULATOR (CFTR) MODULATOR THERAPY IN INFANTS


Summary
The study evaluates the effects of ivacaftor therapy, on infants between the age of 12-24 months of age with cystic fibrosis and a CFTR gating mutation. In this trial the safety of ivacaftor was examined in this young age group. In addition, sweat chloride concentration and exocrine pancreatic function were assessed. In this study the drug is well tolerated and treatment with ivacaftor was associated with a significant decrease in sweat chloride concentration. In the majority of infants, treatment with ivacaftor was also associated with improvements in a number of biomarkers of exocrine pancreatic function including fecal elastase -1, immunoreactive trypsinogen, lipase and amylase.

TREATMENT OF EARLY PSEUDOMONAS INFECTION IN CYSTIC FIBROSIS


Summary
The study tested the hypothesis that the addition of azithromycin to inhaled tobramycin therapy in children...
with early Pseudomonas aeruginosa would decrease the risk of pulmonary exacerbations and prolong the time to pseudomonas recurrence. This multicenter double-blind randomized placebo-controlled study followed subjects for 18 months. Participants who were between the ages of 6 months and 18 years were given azithromycin or placebo three times a week in addition to their standard inhaled tobramycin. The study found that there was a marked decrease in pulmonary exacerbations in the group treated with azithromycin (>40%), and weight increased by > 1 kg when on azithromycin. However there was no significant change observed in microbiology.

Comments
1. There were no safety concerns when taking azithromycin.
2. Subjects had fewer pulmonary exacerbations when on Azithromycin then when on inhaled tobramycin alone.
3. Subjects had increased weight gain on Azithromycin compared to inhaled tobramycin alone.
4. There was no added benefit when compared to inhaled tobramycin alone with regard to microbiology.

CYSTIC FIBROSIS RELATED DIABETES


Summary
This study examines the effects of prolonged ivacaftor therapy on glucose tolerance and insulin and incretin secretion in a small cohort of patients. A number of parameters were examined before and after starting ivacaftor. Spirometry, oral glucose tolerance test, mixed meal tolerance tests glucose potentiated arginine tests and plasma insulin, C peptide, glucagon-like peptide-1, and total glucose dependent insulinotropic polypeptide were measured. The investigators found that there was improved insulin secretion and glucagon secretion suggesting improved beta cell function.

AIRWAY EPITHELIAL HIERARCHY


Summary
Investigators study the cellular composition and hierarchy of the mouse trachea using state of the art single cell RNA sequencing methods and in vivo lineage tracing and describe a unique cell type that expresses extremely high amounts of CFTR. This very unique cell is referred to as the airway ionocyte. The ionocyte is also present in human airways. This cell type is very rare comprising less than 1% of the total cells in the airway. The investigators go on to describe the lineage of multiple other airway cell types including club cells tuft cells ciliated cells and goblet cells. These approaches provide the community with cell-type specific expression programs that will highlight key disease genes and provide insight into the origins of airway disease.

OTHER ARTICLES OF INTEREST


UPDATE IN THE MANAGEMENT OF AERODIGESTIVE PROBLEMS IN THE PULMONARY CLINIC

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STRUCTURE AND FUNCTIONS OF AERODIGESTIVE PROGRAMS


Summary
Aerodigestive programs provide coordinated care for children with complex conditions affecting breathing, swallowing, and growth. While there has been a tremendous growth in the number of aerodigestive programs across the country, there is a lack of consensus in the definition of an aerodigestive patient, structure and function of aerodigestive programs, and research priorities in aerodigestive medicine. The Delphi method was used to generate a multidisciplinary and multi-institutional consensus statement from 33 specialists at 11 established aerodigestive programs. There was nearly 100% response, and consensus was achieved for virtually all items. An aerodigestive patient is defined as “a child with a combination of multiple and interrelated congenital and/or acquired conditions affecting airway, breathing, feeding, swallowing, or growth that require coordinated interdisciplinary diagnostic and therapeutic approach to achieve optimal outcomes.” Essential team members for all patients included a care coordinator, gastroenterologists, nurses, otolaryngologists, pulmonologists, and speech-language pathologists. Essential procedural skills for pulmonologists participating in aerodigestive programs include BAL, bronchial brushing, TEF identification, fiberoptic intubation, sleep state bronchoscopy, endobronchial biopsy, foreign body removal, and balloon dilation; essential skills were also defined for gastroenterologist and otolaryngologists. Further, the structure and function of an aerodigestive program, research priorities and key outcome measures are also identified.

Comments
1. This is the first report to define an aerodigestive patient as well as the structure and function and research and outcome priorities for aerodigestive teams.
2. Identification of key outcomes and research priorities will help to develop clinical guidelines, standardize care, and improve quality.
3. The strength of this study is the use of experienced providers from multiple disciplines and institutions, high response rate, and ability to achieve consensus.
4. The primary weakness of this study is the lack of available data from which to make recommendations, though this presents an opportunity for future investigations.

HEALTHCARE OUTCOMES IN AERODIGESTIVE


Summary
Children with special health care needs have disproportionate health care utilization and incidence of hospitalization; however, there is little evidence that evaluates the efficacy of multidisciplinary aerodigestive programs in the management of complex patients. This was a retrospective cohort with 113 children that evaluated hospital admissions before and after enrollment in a multidisciplinary aerodigestive clinic. All causes of hospital admissions and aerodigestive specific admissions were assessed. Children enrolled in the study had a broad range of aerodigestive disorders, and the majority of subjects (52.2%) were under 5 years of age. While there was not a significant decrease in hospital admissions, total hospital days were reduced by 4.1 days/year, and there was a reduction in hospital days by 6.8 days/year related to aerodigestive conditions.

Comments
1. Multidisciplinary aerodigestive programs can result in decreased hospital days for children with special health needs.
2. This study supports that aerodigestive programs can have a positive impact on patient outcomes and cost of health care.
3. The lack of a control group not enrolled in an aerodigestive program and retrospective review are the primary limitation of this study.

Boesch RP, Balakrishnan K, Grothe RM, Driscoll SW, Knoebel EE, Visscher SL, Cofer SA. Interdisciplinary Aerodigestive Care Model Improves Risks, Costs, and...
Aerodigestive patients have complex and interrelated disorders that affect the airway, breathing, swallowing and growth. The care of an aerodigestive patient is similarly complex and costly. This is a retrospective review of aerodigestive patients who were evaluated and treated before and after the inception of a multidisciplinary aerodigestive program. The electronic medical record was reviewed to determine elements of patient care and evaluation, and the cost of care was assessed using the Mayo Clinic Cost Data Warehouse methodology. There were 38 patients enrolled in this study. Patients enrolled in a multidisciplinary aerodigestive program had decreased time to diagnosis (6 vs 150 days), fewer radiation exposures (2 vs 4), and fewer anesthetic episodes (1 vs 2). There was a 41% reduction in the cost of medical care after development of a multidisciplinary aerodigestive program ($6,055 vs $10,374).

Comments
1. This study highlights that multidisciplinary aerodigestive clinics can improve healthcare efficiency, decrease risk, and decrease cost.
2. The cost of care and patient outcomes following the initial diagnosis is not described.
3. While the study is a natural experiment, the primary limitation is the lack of a control group and single-center design.

TREATMENT OF TRACHEOMALACIA

Summary
Tracheomalacia is often associated with esophageal atresia and is characterized by dynamic collapse of the trachea. Posterior tracheopexy can prevent intrusion of the trachealis and has shown promise as a treatment of tracheomalacia in small, short-term trials. This was a retrospective series of patients with esophageal atresia who had a posterior tracheopexy for severe tracheomalacia—either at the time of the initial esophageal atresia repair (primary treatment) or after the initial repair for chronic respiratory symptoms (secondary treatment). Tracheomalacia was scored based on standardized endoscopic evaluation, and respiratory symptoms were identified from clinic visits. A total of 118 subjects underwent posterior tracheopexy, with 100 (85%) being secondary treatment. Posterior tracheopexy resulted in improvement in tracheomalacia score based on bronchoscopy for both the primary and secondary treatment. Similarly, both groups had improvement in clinical symptoms such as cough, respiratory distress, cyanotic spells, and brief unexplained events. Subsequent surgical interventions were necessary in 15 (13%) of patients.

TREATMENT OF DYSPHAGIA

Summary
There is growing concern that proton pump inhibitors (PPIs) may increase the risk of pulmonary and gastrointestinal infections in children and adults; however, PPIs are frequently prescribed for children with dysphagia due to concern of acid-related lung injury. This was a retrospective cohort study of children under 2 years of age with a diagnosis of dysphagia based on aspiration or penetration during videofluoroscopic swallow study. PPI exposure was based on medication prescription and physician notes. Hospitalizations were stratified by total, urgent pulmonary, and urgent gastrointestinal hospitalizations. Propensity score analysis was used to insure robustness of the analysis. There were 293 subjects enrolled in this study. Aspiration was identified in 156 (53%), and laryngeal penetration in 137 (47%). Nearly half of the subjects had at least one hospitalization. Children treated with PPIs were more likely to be admitted to the hospital (HR= 1.25) and had a nearly 2-fold increase in hospitalization frequency (IRR=1.77) even after adjusting for comorbidities and propensity weight for severity of dysphagia. Similarly, there was a more than 2-fold increase in hospital admission nights (IRR=2.51).

Comments
1. These results highlight that PPIs are commonly used in children with dysphagia and may result in increased morbidity characterize by increased hospitalizations and hospital length of stay.
2. The use of propensity score analysis and adjustment for multiple potential confounder increases the robustness of the findings.
3. This study is limited by its retrospective nature and by only including children under 2 years of age.

OTHER ARTICLES OF INTEREST


ADVANCES IN MANAGEMENT OF OSA


Summary

Hypoglossal nerve stimulation (HGNS) has been shown to successfully treat adults with OSA specifically in those with an apnea-hypopnea index (AHI) between 20-50 events per hour and a BMI of <32 kg/m2 (Strollo PJ Jr, NEJM, 2014). More than 60% of adolescents with Down syndrome (DS) will have significant, persistent OSA despite an adenotonsillectomy. This pilot study evaluated HGNS in 6 youth with DS with refractory OSA. Inclusion criteria were BMI <32kg/m2, AHI between 10-50/hour and CAI of <25% and no evidence of circumferential airway collapse as per drug induced endoscopy. Once the device was activated, follow up PSGs were performed at 2, 6, and 12 months. Primary outcome was AHI; secondary outcome was QOL using OSA-18. The device was able to record hours used per week.

Six patients (4 male), aged 12-18 years of age were included in the study. At 6-12 months, all 6 patients demonstrated improvement with a 56-85% reduction in AHI with residual AHI in the mild to moderate range. At follow-up, the mean duration of use was 5.6-10 hours per night. All patients demonstrated an improvement in QOL scores. Improved sleep patterns were observed with emergence of REM sleep in 3 patients.

Comments

1. HGNS represents an exciting potential therapeutic option for some of the most difficult to treat patients with OSA.
2. Adverse effects included readmission for mild cellulitis of chest requiring antibiotics and one patient was admitted for pain and discomfort requiring narcotics.
3. Data only available for one-year follow-up, long-term efficacy data is required.
4. Highly selected group; there is a need to understand how applicable these data would be to an adolescent cohort with other co-morbidities e.g. obesity
5. Expensive, resource intensive therapy and long-term studies will need to address cost-effectiveness.

ALTERNATIVES TO CPAP THERAPY FOR CHILDREN WITH PERSISTENT OSA


Summary

Continuous positive airway pressure (CPAP) is the mainstay of therapy for persistent OSA. CPAP usage in the pediatric population has increased 3-fold in the past decade. CPAP is an efficacious therapy for OSA but limited by adherence rates of <50% in the pediatric population. This study addresses CPAP alternatives for management of pediatric OSA using high flow nasal cannula therapy (HFNC). Subjects (n=10) intolerant to CPAP (6 males, mean age 10 years and mean BMI percentile 58%) were prospectively recruited. Underlying co-morbidities included Down syndrome, craniofacial syndromes and obesity. All subjects had an in sleep-lab HFNC titration study with initial flow of 5 or 15 L/min for pediatric or adult-sized cannula respectively, and titrated until either 1) resolution of OSA or 2) maximum flow rates achieved on HFNC (20 L for pediatric cannula and 50 L for adult cannula). Compared to the diagnostic baseline PSG data, HFNC at optimal flow rates reduced AHI from 11.1 to 2.1 events per hour, reduced the oxygen desaturation index and decreased the maximum tcCO2. However, 4/10 patients required supplemental oxygen despite maximal HFNC flow rates. HFNC may be a promising alternative for CPAP intolerant patients.

Comments

1. HFNC is not licensed for the use of OSA treatment in adult or pediatric population.
2. HFNC was well tolerated with no reported adverse events after one night.
3. Unclear whether symptoms of OSA and morbidity associated with OSA disease improves with long-term use of HFNC and a rigor-
NOVEL PHARMACOLOGICAL THERAPEUTICS FOR OSA

Summary
Recently, there is evidence to suggest that sleep-related hypotonia of the pharyngeal muscles is related to the central reduction of norepinephrine from wakefulness to sleep and REM related hypotonia is due to an inhibitory effect of acetylcholine through muscarinic receptors. To date, there are no pharmacological treatments for OSA. This study was a randomized, placebo controlled double blind crossover trial to evaluate the effectiveness of Atomoxetine (norepinephrine reuptake inhibitor) and Oxybutynin (an anti-muscarinic) on OSA severity and genioglossus activity in subjects with OSA. Subjects were randomized to either placebo or a combination of Atomoxetine and Oxybutynin 30 minutes before lights out with simultaneous PSG. Subjects had placement of esophageal catheter and intramuscular electrodes in the genioglossus muscle. Patients were asked to sleep in supine position.

Majority of the subjects were male (16/20), with a mean age of 53 years and BMI of 34.8 kg/m2. The mean AHI in the placebo group and Ato-oxy group was 28.5 and 7.5 events per hour respectively (p<0.001). There were significant improvements in the ODI and nadir SaO2 in the treatment group vs placebo. There was a significant increase in genioglossus muscle responsiveness in the Ato-oxy group compared to placebo.

Comments
1. This study provides exciting, novel data of the potential for pharmacological interventions for the management of OSA in adults.
2. The combination of the Atomoxetine and Oxybutynin are believed to have synergistic effects on upper airway dilator muscles. Atomoxetine and Oxybutynin alone did not result in a significant reduction in AHI.
3. There were no significant changes in sleep architecture and arousal index between the groups.
4. Data has to be interpreted with caution given that this is a proof of concept physiological trial. Prolonged use of these pharmacological agents on the impact of OSA and symptoms are unknown. Future studies will also have to address the long-term risks and adverse effects of pharmacological agents.
5. While these data are unlikely to be extrapolated to children in the very near future, pharmacological approaches for OSA is an exciting area of future research.

PERSONALIZED SURGICAL MANAGEMENT OF OSA USING DISE

Summary
DISE is a 3-dimensional assessment of the upper airway (UA) under unconscious sedation and is used to characterize the location and pattern of the UA obstruction. DISE has mostly been used to evaluate UA obstruction following an adeno-tonsillectomy. This study evaluated the role of DISE in mostly healthy children diagnosed with OSA regardless of whether adenotonsillectomy had previously been performed. In the study, 150 children presenting to ENT clinic with suspected OSA had 1) PSG 2) Chervin PSQ 3) ENT exam (grading of tonsils) and 4) DISE. DISE was performed by the same endoscopist with a baseline plan to undertake an adenotonsillectomy (AT). The population was divided into 3 categories; 1) Conventional OSA – no previous surgery with AHI >0 and AHI <10 with variable tonsil size, 2) Disproportional OSA – AHI >10 and no previous surgery or AHI >3 with tonsils < size 3 and no surgery for OSA and 3) Persistent OSA – AHI >3 and previous AT surgery for OSA. All patients in conventional group (n=88) underwent tonsillectomy and 80/88 underwent adenoidecetomy. Of these 4/88 had a chance in management due to DISE – 3 had tongue base reduction and one had pharyngoplasty. For the disproportional OSA group (n=40), all had tonsillectomy and adenoidecetomy and 7/40 had a chance in the surgical management plan. For the persistent OSA (n=22), 16/22 had additional surgery, including tongue base reduction, inferior turbinate surgery and pharyngoplasty. Overall 37% of otherwise healthy children patients had a change in final surgical plan following DISE.

Comments
1. DISE is a safe procedure but could not be completed in 17 cases due to tonsillar obstruction, secretions and inability to reproduce apnea during sedation.
2. Tonsillectomy and/or adenoidecetomy should be considered first line surgery in traditional OSA cases.
3. No PSG data post-surgery to evaluate effectiveness and relevance of DISE and surgery.
4. In this cohort of mostly healthy children, advanced surgery occurred mostly in patients with persistent OSA.
DISE FOR TREATMENT OF OSA IN CHILDREN WITH UNDERLYING COMPLEXITY


Summary
The aim of this study was to determine the effectiveness of DISE directed surgery for infant OSA or persistent OSA post adeno-tonsillectomy (AT). Two groups of children were evaluated pre and post DISE+surgery with PSG; 1) Children with persistent OSA after AT or 2) infants with OSA. Response to surgery was defined as an obstructive AHI of <5 events per hour (if baseline AHI was >5 events per hour) or AHI <1 event per hour (with baseline AHI of <5 events per hour). There were 56 patients (34% were female) with a mean age of 5.5 ±5.5 years of which the majority were Caucasian. There were multiple co-morbidities including laryngomalacia, Down syndrome, Pierre Robin and developmental delay. The mean AHI was 14.9 per hour and most of these, 47/56, had AHI >5 events per hour. The most common surgeries were adenoectomy (48%), tonsillectomy (27%), supraglottoplasty (37.5%) and lingual tonsillectomy (12.5%). Other surgeries included UPP, posterior mid-line glossectomy, mandible distraction and one patient had a tracheostomy. Overall, the mean OAHI changed from 14.9 ± 13.5 to 10.3±16.2 and SaO2 nadir increased from 82.4%+10.2 to 80.1 ± 9.6%. Specifically after surgeries, 18% had complete resolution of OSA, 37.5% had mild residual OSA, but 27% still had persistent severe OSA.

Comments
1. DISE directed surgery was significantly more effective for children without previous AT e.g. infants with OSA.
2. DISE was more effective in subjects with lower OAHI suggesting that multilevel collapse is more difficult to effectively treat with surgery.
3. Black race was associated with a lower likelihood of response.
4. Need to further understand who is most likely to benefit from DISE targeted surgery.

OTHER ARTICLES OF INTEREST


UPDATE ON PCD AND NON-CF BRONCHIECTASIS

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TREATMENT OF BRONCHIECTASIS EXACERBATIONS


Summary
Antibiotic therapies for acute respiratory exacerbations have not been prospectively studied in children with non-cystic fibrosis (non-CF) bronchiectasis. Despite this, therapeutic guidelines recommend twice daily oral amoxicillin-clavulanate as first line therapy for non-CF bronchiectasis respiratory exacerbations, though compliance may be superior with a once daily medication, such as azithromycin. This prospective, randomized, double blind, placebo controlled trial examines the resolution of acute cough in 179 children with outpatient, non-CF bronchiectasis respiratory exacerbations receiving 21 days of either oral amoxicillin-clavulanate (45 mg/kg/day) or oral azithromycin therapy (5mg/kg/day). Results show azithromycin is non-inferior to amoxicillin-clavulanate for resolution of cough during a non-CF bronchiectasis respiratory exacerbation (77% cough resolution at day 21 with either agent). However, children randomized to oral amoxicillin-clavulanate had a faster resolution of cough versus azithromycin (median 10 versus 14 days). Compliance was excellent and similar in both medication groups. Children taking azithromycin had a greater proportion of azithromycin resistant nasal organisms at the end of therapy versus those taking amoxicillin-clavulanate (80% versus 29%). There are no significant differences in inflammatory markers, time to next exacerbation, pulmonary function, or quality of life markers in children treated with either agent. Sub-group analysis of children on long term antibiotic therapy prior to and during study period did not show significantly different outcomes.

Comments
1. Twenty one days of either azithromycin (5mg/kg/day) or amoxicillin-clavulanate (45 mg/kg/day) are equally effective therapies for cough resolution in children with non-CF bronchiectasis, yet higher dose amoxicillin component (80mg/kg/day) and azithromycin (up to 10mg/kg/day) may generate different clinical outcomes.
2. Faster resolution of cough with amoxicillin-clavulanate therapy over azithromycin may translate to less missed school/work days and ultimately affect quality of life.
3. Long term effects of increased azithromycin resistant organisms (such as S. aureus) at the end of prolonged azithromycin therapy require further clinical investigation.
4. While compliance with a once daily medication, like azithromycin, seems intuitively superior, this is not the case when studied in a double dummy trial of children with non-CF bronchiectasis, though compliance outside of a clinical trial environment may still be superior with a once daily medication.

ADOLESCENT OUTCOMES IN PEDIATRIC BRONCHIECTASIS


Summary
Chronic suppurative lung disease (CSLD) and bronchiectasis are common in indigenous populations, including Alaskan Native (AN) children from the Yukon Kuskokwim Delta region. Older studies report an adolescent “honeymoon period” of decreased respiratory symptoms in children with bronchiectasis, but this trend has not been recently examined.

This long-term analysis examines clinical outcomes in 34 AN adolescents (median age 11.8 years) with CSLD or bronchiectasis. At a median follow up of 12 years, CT scans show 14 (41%) with bronchiectasis, 8 (24%) with CSLD lacking bronchiectasis, and 12 (35%) who did not clinically require CT scan. Nearly 80% of children were symptomatic with an abnormal physical examination and/or cough, wheeze, or respiratory exacerbation in the prior 12 months. Half of the subjects had abnormal chest exams, and crackles were more prevalent with confirmed bronchiectasis. Sixty-four percent have obstruction on spirometry, with lower FEV1/FVC values in confirmed bronchiectasis. Despite these findings, there are less episodes of lower respiratory tract infection (LRTI) requiring antibiotics or hospitalization.
in adolescence versus childhood, though 45% report missing school for respiratory illness in the past year, and the median of 32 lifetime episodes LRTI treatment remains quite elevated. Overall, the incidence of bronchiectasis is decreasing in AN children, from 18 cases per 1000 births in the 1980’s to 6.7 cases per 1000 births in the 2000’s.

Comments
1. While the severity and frequency of lower respiratory tract exacerbations improve during a “honeymoon period” in AN adolescents with CSLD and bronchiectasis, significant disease burdens persist at baseline with abnormal lung function, abnormal physical exam findings, and school absenteeism for respiratory reasons.
2. Despite this persistence of lung disease in AN adolescents with CSLD and bronchiectasis, the number of prescribed antibiotic courses remains low, possibly reflecting the difficulties in regular medical follow up for this fragile and maturing population.
3. Despite a honeymoon period in adolescent CSLD and bronchiectasis, regular clinical follow up is essential to monitor for lower respiratory disease progression, which may have profound long-term effects if ignored.
4. Access to medical care, vaccines, and clean drinking water seem to have improved the bronchiectasis incidence in AN children of the Yukon Kuskokwim Delta region.

DIAGNOSIS OF PRIMARY CILIARY DYSKINESIA

Summary
Primary Ciliary Dyskinesia (PCD) is difficult to diagnose as no single test detects all forms of this disease, and certain diagnostic tests (ciliary transmission electron microscopy (TEM) and high speed videomicroscopy (HSVM)) require expertise to correctly perform and interpret test results. Four PICO questions on nasal nitric oxide (nNO), extended panel genetic testing of >12 PCD genes, HSVM, and ciliary beat frequency (CBF) are researched, and diagnostic accuracy for each test is compared against a reference standard of classic TEM ultrastructural defect and/or 2 genetic mutations in a known PCD gene.

In order to maximize diagnostic accuracy, only patients with appropriate PCD clinical phenotypes (often including year-round wet cough since infancy, year-round nasal congestion since infancy, neonatal respiratory distress, or an organ laterality defect) are included. In patients with strong PCD phenotypes, both nasal nitric oxide measurement and extended genetic panel testing of >12 PCD genes are the most standardized, feasible, and accurate PCD diagnostic tests that are currently available (nNO testing sensitivity 96%, specificity 96%; extended panel genetic testing sensitivity 80%, specificity 99.5%). HSVM testing is not recommended as sample preparation procedures and interpretation of test results are non-standardized and too subjective to provide reliable diagnostic accuracy at present. CBF analysis should also be avoided due to poor diagnostic accuracy compared against the reference standard.

Comments
1. The North American PCD clinical diagnostic tests of choice are now nNO measurement and extended genetic panel testing, while ciliary motility assessments should remain in research settings until standardized methodology and interpretation techniques are available across clinical centers.
2. Nasal nitric oxide testing has limitations, as it can be artificially decreased by other issues (like acute viral respiratory infection or cystic fibrosis), and repeat nNO values on separate occasions, with cystic fibrosis ruled out, are required to make a PCD diagnosis.
3. Nasal nitric oxide values can rarely be normal with certain PCD genotypes, so negative nNO results do not “rule out” PCD in cases where the PCD phenotype is very strong.
4. Widespread use of nNO testing in populations without strong PCD phenotypes will result in much worse diagnostic accuracy than reported here.
5. As more genes causing PCD are discovered, the diagnostic accuracies of all other tests will likely worsen as genetic testing accuracy improves.

CILIARY MOTILITY ANALYSIS IN PCD

Summary
High-speed videomicroscopy analysis (HSVM) of ciliary motility is recommended for PCD diagnosis in European Respiratory Society (ERS) guidelines. However, this technique requires ultra-specialized testing methods at
highly experienced centers after lengthy air-liquid interface culture to regrow ciliated cells. In this retrospective analysis of 120 randomly selected HSVM patient samples from three British PCD centers, three blinded HSVM experts compare HSVM results against two reference standards: 1) ERS guideline recommendations using only TEM and/or PCD genetic testing, or 2) a multidisciplinary team (MDT) diagnostic opinion using all available diagnostic results, including previous HSVM interpretations. Importantly, disease control samples are not intentionally included in analyzed HSVM samples.

Results of HSVM show high diagnostic accuracy compared to ERS guideline PCD diagnosis (sensitivity 100%, specificity 96%), but when including 42 inconclusive HSVM results (35% of the total population), results are less accurate (sensitivity 93%, specificity 68%). However, HSVM is mainly compared against TEM results alone, as only 16 subjects (13%) had PCD genetic testing. Compared against past MDT opinion, HSVM seems very accurate (sensitivity 97%, specificity 91%), but worsens considerably when counting 25 inconclusive HSVM cases (sensitivity 85%, specificity 68%).

There is good inter-observer agreement between three HSVM experts on cases where HSVM is clearly diagnostic of PCD (K=0.70), but agreement worsens considerably when HSVM results are non-diagnostic (K=0.44 for “PCD highly unlikely”; K=0.11 for “PCD highly likely”; K=0.20 for “inconclusive”).

Comments
1. The diagnostic accuracy of HSVM seems excellent in a highly selected population, yet this accuracy is likely substantially inflated due to several critical errors in methodology (only limited genetic testing in the ERS guideline reference standard, inclusion of HSVM in both the index test and MDT reference standard, and lack of other disease controls).
2. Accurate comparison of HSVM against a true PCD reference standard of TEM and/or genetic testing in all included subjects is lacking here, and the true diagnostic accuracy of HSVM in the era of PCD genomic sequencing remains unknown.
3. The lack of air-liquid interface culture to regrow ciliated cells prior to HSVM analysis in this study, despite a strong recommendation to do so in ERS PCD guidelines, means some abnormal HSVM results may be due to secondary insults and not of primary (genetic) origin.
4. While inter-observer agreement among HSVM experts is good in definitive PCD, agreement is considerably weaker when HSVM is not definitively diagnostic of PCD.
5. HSVM remains a research-based PCD test with non-standardized sample preparations, subjective interpretation of results without established minimal diagnostic criteria, and no prospective evidence of successful transferability to centers lacking experience in this technique.

GENOTYPE PHENOTYPE ASSOCIATIONS IN PCD

Summary
With over 40 different PCD genes, certain genotypes may result in worse clinical phenotypes. Past cross-sectional data suggests PCD patients with absent inner dynein arms, central apparatus abnormalities, and microtubule organization (IDA/CA/MTD) or corresponding CCDC39/CCDC40 gene mutations have worse lung function and nutritional parameters. This multi-center, longitudinal study tracks children <19 years old with PCD from mutations in 22 different genes and various ciliary ultrastructural defects, collecting annual lung function, sputum cultures, and other phenotypic information. Over 5 years, 137 participants completed 732 visits, and clinical trends of various PCD subtypes are compared against those with absent ODA or corresponding gene defects in ODA proteins (ODA controls). As a group, all PCD patients have a -0.57% predicted annual decline in FEV1 over the study period. Participants with ICA/CA/MTD and/or CCDC39/CCDC40 mutations are diagnosed at younger ages, have worse FEV1 at enrollment (72% versus 88% predicted), and exhibit a steeper annual decline in FEV1 over 5 years (-1.1% versus -0.73% predicted) compared against ODA controls, respectively. Body mass index is worse at enrollment for patients with IDA/CA/MTD or CCDC39/CCDC40 mutations versus ODA controls but does not decrease further over the study. There are no significant differences in pathogen prevalence per ultrastructural defect or PCD gene mutation, and persistent P. aeruginosa infection rates are low (9%) in this young PCD cohort.

Comments
1. Patients with PCD from IDA/CA/MTD and/or CCDC39/CCDC40 mutations have worse pulmonary function and nutrition from early in life and may benefit from more aggressive pulmonary and nutritional therapies at younger ages.
2. Regular PCD therapies (daily airway clearance, sputum surveillance, antibiotics, etc.) after diagnosis seem to stabilize lung function over time in most forms of PCD, yet specific treatment differences and subsequent clinical benefits have not yet been examined in a longitudinal fashion.
3. Though classically considered to have milder lung disease than cystic fibrosis cohorts, PCD patients seem to have worse lung function than contemporary cystic fibrosis populations of similar age.
4. Persistent pseudomonas infection rates are relatively low in a young PCD cohort, yet these do increase with age, and reasons for this difference from cystic fibrosis cohorts require comparative study of cough clearance, mucus rheology, and innate immune defenses.

OTHER ARTICLES OF INTEREST

Primary Ciliary Dyskinesia: Diagnosis


Primary Ciliary Dyskinesia: Phenotype

Primary Ciliary Dyskinesia: Radiology


Non-CF Bronchiectasis: Review

Non-CF Bronchiectasis: Physical Activity

Non-CF Bronchiectasis: Preventative Vaccination
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