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UPMC Children's Hospital of Pittsburgh is affiliated with the University of Pittsburgh School of Medicine and nationally ranked in nine clinical specialties by *U.S. News & World Report*.

Sometimes the Lungs Take the Back Seat: A Pediatric Case of Pancreatic Cystosis and Cystic Fibrosis Biliopathy

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Case Presentation

The patient is a 14-year-old woman with cystic fibrosis (CF) with mild lung disease (FEV₁ 111%) and pancreatic insufficiency who presented with abdominal and low back pain.

The patient reported three weeks of intermittent, crampy, progressively worsening lower abdominal pain that radiated to the back. The pain was exacerbated by eating and movement, and improved with over-the-counter pain medications. Associated symptoms included decreased appetite and activity level, nausea, vomiting, bloating, and weight loss. She was having large, infrequent bowel movements with occasional streaks of blood. She had regular menstrual cycles with rare dysmenorrhea. The patient denied abdominal trauma, fevers, diarrhea, dysuria, urinary urgency or frequency, hematuria, or flank pain.

Initial Evaluation and Management

The patient was referred to our center after an abdominal CT with intravenous contrast demonstrated a right hemorrhagic ovarian cyst and complete replacement of the pancreas by innumerable cysts of varying sizes. Additionally, mild intrahepatic biliary ductal dilatation was noted and was greater in the left hepatic lobe. Her exam was significant only for tenderness in the bilateral lower abdominal quadrants. Laboratory evaluation included normal electrolytes, transaminases, bilirubin, gGTP, lipase/amylase, and white blood cell count. Her albumin and hemoglobin were low at 2.8 g/dL (NL 3.8-5.4) and 11.1 g/dL (NL 12-16), respectively, and platelets were elevated at 789 10⁹/L (NL 156-369). She was admitted for further evaluation of her abdominal pain and the cystic mass. A bowel

Pancreatic Cystosis and Cystic Fibrosis Biliopathy *Continued from Page 1*

regimen was started, her abdominal pain improved, and she was subsequently discharged to her home. As an outpatient, she was started on oral contraceptive pills for management of her ovarian cysts.

Follow-up Evaluation and Management

During outpatient follow-up, the patient continued to have intermittent abdominal pain. Celiac serologies and stool calprotectin were normal. A hepatic function panel checked in the interim remained normal, and abdominal ultrasounds showed stable pancreatic cysts and biliary tree dilatation. Ten months after her initial hospitalization, she was admitted for a pulmonary exacerbation. During this stay, she acutely developed scleral icterus, jaundice, and pruritus. Labs were significant for a direct hyperbilirubinemia (total bilirubin 6.9 mg/dL, direct 5.8 mg/dL), and elevated gGTP, AST, and ALT (335 U/L, 510 U/L, 382 U/L, respectively). An abdominal ultrasound demonstrated increased biliary ductal dilatation and gallbladder sludge. A magnetic resonance cholangiopancreatography (MRCP) showed irregular dilatation of the intrahepatic biliary ducts, dilatation of the common bile duct, and persistence of the pancreatic cysts. Ursodiol was started, and her oral contraceptive was discontinued. Her transaminases improved and she was discharged.

Shortly after her discharge, a percutaneous liver biopsy showed evidence of mild cholestasis and a biliary obstructive pattern of injury with mild fibrotic changes. Her bilirubin normalized, but her transaminases and gGTP continued to rise. Five months later, she redeveloped scleral icterus and pruritus and had a repeat MRCP concerning for "sclerosing cholangitis" with beaded, dilated intrahepatic bile ducts (Figure 1).

Discussion

Pancreatic Cystosis in CF

Abnormal pancreatic imaging is common in patients with CF, with several patterns of radiographic findings noted that include normal pancreas, partial or complete fibrofatty replacement, and pancreatic atrophy.¹ Pancreatic cystosis, however, is a rare entity characterized by complete replacement of the pancreas with epithelial-lined macrocysts of varying sizes. The pathophysiology of pancreatic cystosis is postulated to be defective bicarbonate secretion inherent to CF. The bicarbonate transport defect leads to inspissated secretions, increased fluid pressure proximal to the obstruction, expansion of the pancreatic ducts, and eventually transformation into cysts of various sizes.²

Pancreatic cystosis is typically discovered incidentally with ultrasound (US) or magnetic resonance imaging (MRI) during evaluation of abdominal pain. While some advocate that MRI is the most accurate imaging method for evaluating the cysts and surrounding structures,³ others have noted that MRI may not contribute additional information beyond US.¹

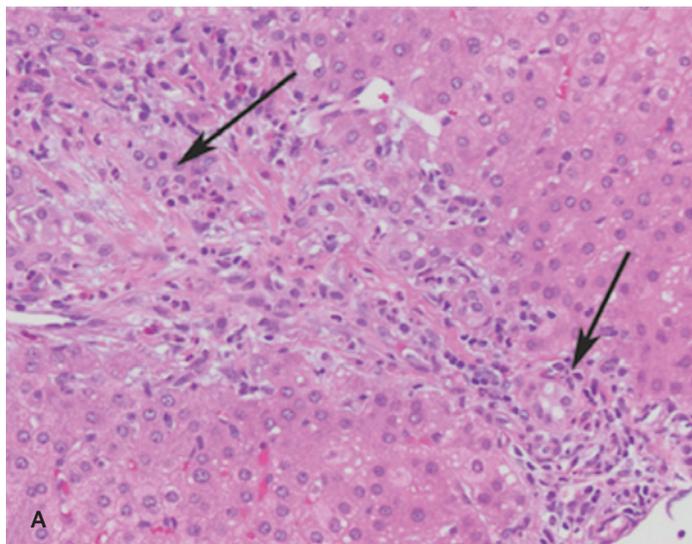


Figure 1: Abdominal Imaging and Liver Histology: (A) Liver core biopsy showing representative portal tract with edema and a mixed inflammatory infiltrate that contains numerous neutrophils and occasional eosinophils. Bile ducts show evidence of mild damage (arrows) (HE, 200X). Other areas showed mild pericentral cholestasis and mild portal and central fibrotic changes (not shown). **(B)** Axial CT image of complete replacement of pancreas with cysts.

The differential diagnosis for pancreatic cystosis includes polycystic kidney disease, von Hippel-Lindau disease with pancreatic involvement, microcystic adenoma, mucinous cystic neoplasm, and lymphangioma.² In general, a confirmatory biopsy is considered unnecessary among patients with pancreatic cystosis in the CF population.^{1,3}

Most patients with pancreatic cystosis are asymptomatic. Monitoring with ultrasound or MRI every six to 12 months has been suggested³ although no uniform recommendations exist for management of symptomatic patients. Endoscopic drainage of large cysts and surgical resection have been described.³ Regarding prognosis, no cases of malignant transformation within pancreatic cystosis have been reported.

Liver Disease in CF

CF-related liver disease (CFLD) occurs in about a third of patients with CF and can carry significant morbidity and mortality. Absence of the normal biliary epithelial CF transmembrane regulator (CFTR) protein function is thought to lead to cholestasis, biliary obstruction, periductal inflammation and proliferation, and fibrosis. Phenotypically, patients present most commonly with focal biliary cirrhosis, though steatosis, gallbladder involvement, multilobular cirrhosis, and a biliopathy with a sclerosing cholangitis-type picture also can occur.^{4,5} From an imaging standpoint, CFLD is most commonly evaluated with ultrasound, though for suspected biliary abnormalities, MRCP is the preferred modality.

Concurrent with the diagnosis of pancreatic cystosis, our patient had imaging findings of CF-associated biliopathy. Initially, dilatation of intrahepatic bile ducts was noted with normal serological markers. More recently, an MRCP showed irregular dilatation and beading of intrahepatic bile ducts and dilatation of the common bile duct in the setting of elevated bilirubin, transaminases, and gGTP. In a small study of adults with CF, 38 percent had sclerosing cholangitis-type lesions on imaging.⁵ Prevalence in the pediatric population is unknown. Our patient's liver disease is most likely multifactorial, both from obstruction of bile flow due to her pancreatic cystosis and intrinsic liver disease in the form of a sclerosing cholangitis phenotype.

At this point, the optimal strategy to manage and slow the progression of her liver disease in the setting of her large pancreatic cysts is unknown. Ideally, therapeutic endoscopic retrograde cholangiopancreatography (ERCP) could be used to improve bile flow and slow liver injury, but it could be technically difficult and high-risk for complications given her pancreatic pathology. Pancreatectomy is also considered to be an option. She has not had evidence of decompensated liver disease or portal hypertension to suggest need for liver transplant. A multidisciplinary approach involving hepatology, pulmonology, gastroenterology, and abdominal transplant teams is required for care of these complicated patients.

Conclusions

Pancreatic cystosis is a rare finding in patients with CF and should be considered in the differential diagnosis of those with gastrointestinal symptoms. It is often an incidental finding in the work-up of abdominal pain, so multiple gastrointestinal and non-gastrointestinal etiologies should also be considered. An intrahepatic CF-associated biliopathy is recognized in adults with CFLD, but pediatric data is lacking. Co-existent

biliopathy, recurrent episodes of cholestasis, and pancreatic cystosis has not been previously described and present a unique management challenge requiring a thoughtful team approach.

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Welcome New Faculty Members

The Division of Pulmonology is pleased to announce the appointment of two new faculty members.



Gregory Burg, MD, joined the Division in July. Most recently, Dr. Burg completed his fellowship in Pediatric Pulmonary Medicine at the University of Cincinnati and Cincinnati Children's Hospital Medical Center.



Deepa Burman, MD, joined the Division in June. Dr. Burman will assume the role of co-director of the Pediatric Sleep Program. Dr. Burman is board certified in family medicine and sleep medicine, and has been a faculty member in the Department of Family Medicine at the University of Pittsburgh since completing both her fellowship training and residency at the University of Pittsburgh School of Medicine.

Lung Clearance Index

The **Lung Clearance Index (LCI)** is a pulmonary function measurement that is becoming increasingly utilized in patients with cystic fibrosis (CF). LCI has several attractive features. Measurement is performed during tidal breathing (not requiring forced expiratory maneuvers), and the LCI may be more sensitive to early CF lung disease than spirometry. It is thought to reflect ventilation inhomogeneity and, as such, is a marker of small airway disease (whereas FEV₁ likely reflects disease in larger airways).

The LCI is defined as the number of lung volume turnovers needed to reduce the concentration of a tracer gas by a factor of 40 with tidal breathing. The LCI is one parameter obtained from the Multiple Breath Washout (MBW), historically performed by having the patient tidally breathe a gas mixture consisting of air and a small amount of an insoluble tracer gas (e.g., Sulfur hexafluoride, SF₆) until the inspired and exhaled concentrations equilibrate (wash-in phase). Next, the breathing circuit is switched for the subject to tidally breathe air (washout phase), and the exhaled tracer gas concentration and exhaled volume are measured until the concentration of tracer gas has been reduced to 1/40 of the equilibration concentration (the LCI point).

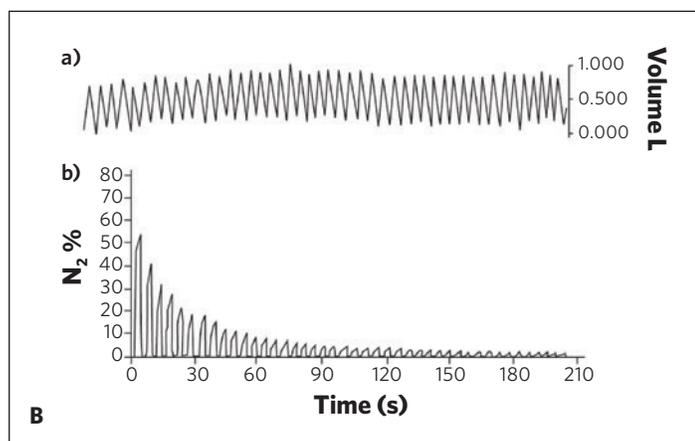
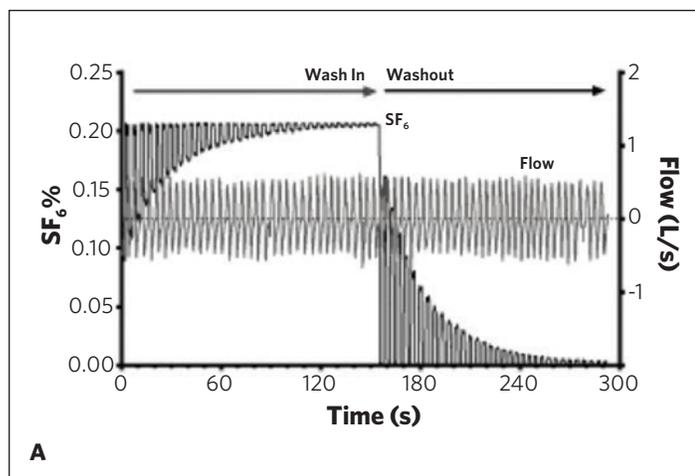


Figure 1: Multiple breath washout curves using SF₆ (A) and nitrogen (B).

LCI is calculated as the cumulative exhaled volume at this point divided by the functional residual capacity (FRC), which is derived from the washout curve of the tracer gas.

The Lung Clearance Index has been used to demonstrate both progression of CF lung disease in young children¹ and the response to several treatments, including mucolytic drugs and airway clearance. Investigators at UPMC Children's Hospital of Pittsburgh have participated in studies demonstrating the effect of CFTR modulator drugs on the LCI.²

Some have proposed using endogenous nitrogen (N₂) as the tracer gas as it is washed out by breathing 100 percent oxygen. The advantage of this methodology is that there is no wash-in required, and oxygen is an inexpensive gas for the testing. There may be some disadvantages as well, and some devices used in clinical trials (e.g., Exhalyzer® D, from ECO MEDICS) are not yet FDA approved. In contrast, MBW with SF₆ may be more expensive, although the sole commercial device for this purpose (Innocor® LCI, from PulmoTrace) is FDA approved.

While the measurement is gaining popularity in clinical trials, there remain several questions, some of which we have been trying to address in our laboratory at Children's Hospital.

First, there has been a longstanding concern that as nitrogen is washed out of the lung, nitrogen from the blood re-enters the lung (this is termed "back diffusion"). This was described to affect nitrogen washout for measurement of lung volume as early as the 1940s.

We undertook MBW tests using a modified setup to simultaneously measure N₂ and SF₆ in healthy young adults.³ SF₆ mixed in air was washed in from a large bag until the gas concentrations stabilized. The patient then was connected to a second bag prefilled with 100 percent oxygen. SF₆ and nitrogen were simultaneously washed out until the concentration of both gases were < 1/40 of the starting concentration. During one MBW test, the subjects were asked to hold their breath for 30 seconds at two different points; the second MBW test was performed while the subjects exercised on a cycle ergometer. Increases in end-tidal nitrogen concentration after the breath holds was assumed to be due to back diffusion, and this increased when subjects increased cardiac output by exercising.

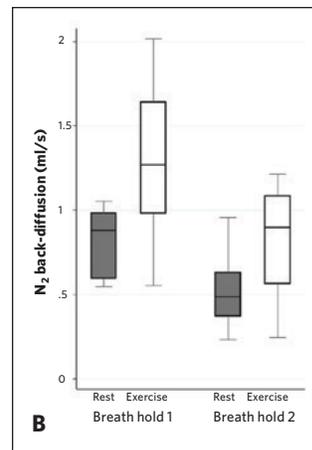
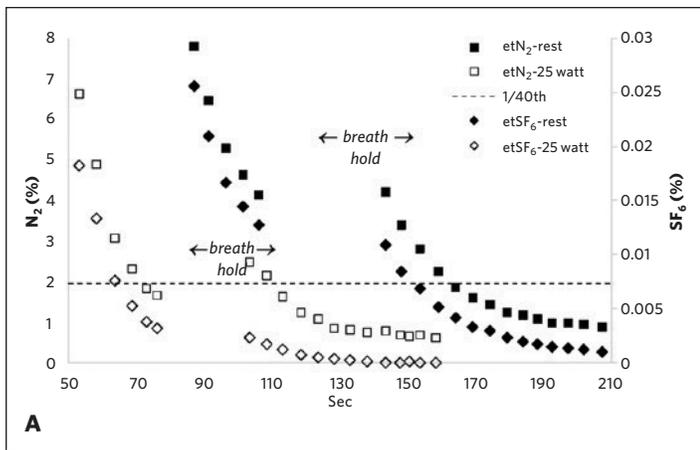


Figure 2: (A) Multiple breath washout of both nitrogen (left axis, squares) and SF₆ (right axis, diamonds) with two breath-hold periods, conducted both at rest (filled symbols) and during low level exercise (open symbols). (B) N₂ back diffusion during the breath holds at rest and during exercise.

We estimated that alveolar nitrogen concentration was about one-third of the total concentration at the LCI point, leading to overestimation of LCI. We concluded that the N₂ LCI point is influenced significantly by back diffusion, which depends on cardiac output and other factors.

We also suspect that other technical factors (besides back diffusion) contribute to differences in LCI measured by nitrogen and SF₆ washout. This may be, in part, that nitrogen is indirectly measured by most devices and is calculated by subtracting the sum of oxygen and carbon dioxide concentrations from 100 percent. The use of these multiple analyzers could create small errors that are amplified at very low concentrations of nitrogen.

In an ongoing study at Children's Hospital, we connected the Exhalyzer breathing assembly (for N₂ washout) to a pneumotach and the gas inlet of the Innocor analyzer (for SF₆ washout). Healthy adult subjects breathed tidally from a 120 L bag with 0.2 percent SF₆ in air to wash-in gas until the concentration was stable, and then the subjects switched to washout of SF₆ and N₂ by breathing 100 percent oxygen from the Exhalyzer bias flow system. Washout curves were recorded by both devices. The lung volume (FRC) values calculated from SF₆ MBW (See Figure 3, orange dotted line) plateau at the end of washout as expected, while the FRC values calculated from N₂ MBW continue to slowly increase (blue dotted line) and were significantly different.

Indeed, the N₂ concentration failed to reach zero even after prolonged washout with 100 percent oxygen, and instead appears to become stable at around one percent.

We suspect that these differences are exacerbated in patients with lung disease, and data collection in patients with cystic fibrosis is ongoing.

In summary, the Lung Clearance Index holds great promise as a sensitive measure of lung disease in cystic fibrosis. Several technical methodologic questions remain regarding choice of tracer gas and analyzers. Given that CF lung disease starts very early, it is hoped that these assessments can be scaled down for measurements in infants and toddlers, and Children's Hospital will be participating in studies in the coming year to determine this.



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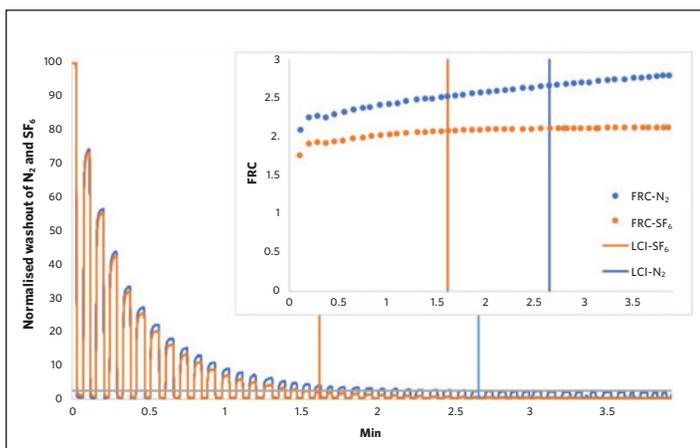


Figure 3

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New Investigator-Led Cystic Fibrosis Research

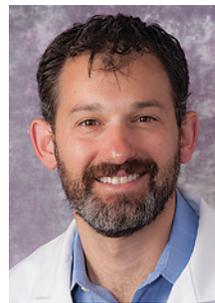
The Division of Pulmonology currently has a number of investigator-initiated clinical studies in progress within its Cystic Fibrosis Center.

One current investigation is an observational study of the sinus and airway microbiome in individuals with cystic fibrosis (CF), led by **Stella Lee, MD**, an otorhinolaryngology specialist with the Department of Otolaryngology, and **Jennifer Bomberger, PhD**, from the Department of Microbiology and Molecular Genetics at the University of Pittsburgh.

A second investigation is a longitudinal study of epithelial physiology in the nose, airway, and sweat glands that seeks to understand the relationship between cystic fibrosis transmembrane conductance regulator (CFTR) function and mucus/liquid clearance in the lung using novel nuclear medicine techniques developed by **Tim Corcoran, PhD**, associate professor of medicine and bioengineering in the University of Pittsburgh School of Medicine with support from other center investigators, including **Michael M. Myerburg, MD**, from the Division of Pulmonary, Allergy and Critical Care Medicine, and **Daniel Weiner, MD**, and **Joseph M. Pilewski, MD**, in the Division of Pediatric Pulmonology.

Additionally, a phase 1b/2a study led by Dr. Pilewski and **Anna Zemke, MD, PhD**, from the University of Pittsburgh Department of Medicine Division of Pulmonary, Allergy and Critical Care Medicine is investigating the safety and efficacy of inhaled sodium nitrate as an antimicrobial agent for individuals with CF.

Collectively, these multidisciplinary studies highlight the collaborations between physicians and scientists specializing in cystic fibrosis at the University of Pittsburgh and the Antonio J. and Janet Palumbo Cystic Fibrosis Center at UPMC Children's Hospital of Pittsburgh.



Top row, from left: Stella Lee, MD; Jennifer Bomberger, PhD; Tim Corcoran, PhD; *middle row, from left:* Mike Myerburg, MD; Joseph Pilewski, MD; *bottom row, from left:* Daniel Weiner, MD; Anna Zemke, MD.

New CME Courses Available for Physicians

Visit UPMCPhysicianResources.com/Pediatrics for the latest CME courses available for physicians, including:

Psychosocial Stress and Asthma

Presenter: Juan Celedón, MD, DrPH

Dr. Celedón reviews the epidemiology and management of psychosocial stress and asthma in children. Part I discusses ethnicity, epidemiology, stress, and asthma. Part II involves epigenetics and bronchodilator response. Part III features PTSD, depression, and asthma. Part IV talks about the role of ancestry and violence. This course is accredited for .75 AMA PRA Category 1 Credits™.

The Power of Telemedicine (remote patient monitoring): A Triple Aim-based Tool in Medicine

Presented by: Andrew R. Watson, MD, MLITT, FACS

Dr. Watson gives a presentation on the three different types of telemedicine: traditional, synchronous, and asynchronous.

About the Cystic Fibrosis Center

The **Antonio J. and Janet Palumbo Cystic Fibrosis Center** (CF Center) at UPMC Children's Hospital of Pittsburgh is dedicated to providing state-of-the-art care to patients and families with cystic fibrosis, offering education for health care professionals, and conducting clinical and basic research in cystic fibrosis. The program is accredited by the Cystic Fibrosis Foundation for clinical care and research. Based on consistently good patient outcomes, our CF Center recently was selected as a benchmarking site from which other programs could learn from our practices.

CF Clinical Trials

The CF Center is involved in 25-30 ongoing clinical trials, including studies sponsored by industry/pharma and CFF Therapeutics. In addition, we have several investigator initiated clinical studies including:

- LIMBUS (Longitudinal Infant Assessment of Multiple Breath Washout Study)
- Hyperglycemia and Other Factors Affecting Recovery of Lung Function During Pulmonary Exacerbations
- Outcomes in Pancreatic Sufficient Patients with Cystic Fibrosis
- Assessment of Glucose Control in Patients with CF Liver Disease

For more information and details about each study, or to refer a patient for study enrollment, please visit CHP.edu/our-services/Pulmonology.

CF Center Clinical Staff

Daniel Weiner, MD – Co-Director

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Recent Publications

Below is a selection of recent publications from Division faculty.

Han YY, Forno E, Shivappa N, Wirth MD, Hebert JR, Celedón JC. The Dietary Inflammatory Index and Current Wheeze Among Children and Adults in the United States. *J Allergy Clin Immunol Pract*. 2018; 6(3): 834-841.

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Sullivan L, Forno E, Pedersen K, Nielsen JG, Weiner DJ. Nitrogen Back-diffusion During Multiple-Breath Washout With 100% Oxygen. *Eur Respir J*. 2017 Sep 9; 50(3).

Kazmerski TM, Sawicki GS, Miller E, Jones KA, Abebe KZ, Tuchman LK, Ladores S, Rubenstein RC, Sagel SD, Weiner DJ, Pilewski JM, Orenstein DM, Borrero S. Sexual and Reproductive Health Care Utilization and Preferences Reported by Young Women With Cystic Fibrosis. *J Cyst Fibros*. 2018 Jan; 17(1): 64-70.

Video Rounds

Video Rounds is a series of short, informative, and educational videos created for physicians and cover a variety of medical and surgical disciplines. The following Video Rounds in Pediatric Pulmonary Medicine are available by visiting UPMCPhysicianResources.com/Pediatrics.

Studying the Correlation Between Vitamin D Levels and Asthma in Children. Presented by Juan Celedón, MD, DrPH.

Pulmonary Function Testing in the Pediatric Population. Presented by Daniel Weiner, MD.

Cystic Fibrosis. Presented by Daniel Weiner, MD.



About UPMC Children's Hospital of Pittsburgh

Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 13th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2017).