NASPGHAN 2017

Single Topic Symposium ✦ Postgraduate Course ✦ Annual Meeting

November 1–4, 2017 ✦ Caesar's Palace ✦ Las Vegas, NV

Frontiers in Pediatric Pancreatology
Wednesday, November 1, 2017
Milano 1 – 2

Course Directors:

Veronique Morinville MD

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Frontiers in Pediatric Pancreatology
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Milano 1 - 2
Course Directors: Veronique Morinville MD, Alvin Jay Freeman MD and Sohail Husain MD

Objectives: The underlying objective of the symposium is to provide the most influential and current research in pediatric pancreatitis and to update the attendees on the numerous and exciting advancements in pediatric pancreatic research. The following areas were identified the key areas of focus in order to meet our objectives, each represented by their own module during the symposium:

1. Risk factors and natural history of pancreatitis in children
2. Pancreatic imaging and pancreatic function tests in children
3. Management of pancreatitis in children
4. New frontiers in pediatric pancreatic research

7:30 – 8:00	Continental Breakfast	Milano 3 - 4

Module 1 - Diagnosis, Risk Factors and Natural History of Pancreatitis In Children
Moderators: Zack Sellers MD and Cheryl Gariepy MD

8:00am – 8:10am	Introduction *Alvin Jay Freeman MD, Emory University*
8:10am – 8:30am	Why do some drugs cause pancreatitis? *Sohail Husain MD, Children's Hospital of Pittsburgh at UPMC*
8:30am – 8:50am	Genetics and the impact of CFTR mutations in pancreatitis *Tanja Gonska MD, Hospital for Sick Children*
8:50am – 9:10am	Emerging data: Evaluation of child with pancreatitis including endoscopy *Quin Liu MD, Cedars Sinai Medical Center*
9:10am – 9:30am	The progression from acute to chronic pancreatitis *Christopher Forsmark MD, University of Florida*
9:30am – 9:50am	Panel Discussion/Questions
9:50am – 10:00am	Break

Module 2 - Pancreatic Imaging and Exocrine Function in Children
Moderators: Denease Francis MD and Victor Fox MD

10:00am – 10:20am	Imaging methods to access the pancreas in children *Andrew Trout MD, Cincinnati Children's Hospital Medical Center*
10:20am – 10:40am	Do's and don'ts of endoscopic pancreatic function testing *Maisam Abu-El-Haija MD, Cincinnati Children's Hospital Medical Center*
10:40am– 11:00am	Diagnosis of PEI and treatment with PERT in 2017 *Mark Lowe MD, Washington University*
11:00am – 11:20am	Panel Discussion/Questions

11:30am – 12:45pm	Lunch/Breakout Sessions	**Milano 3 - 4**

Module 3 - Management of Pancreatitis in Children
Moderators: Madhura Phadke MD and Asim Maqbool MD

12:45pm – 1:15pm	Keynote: Management of AP in adults: Which lessons are applicable to pediatric care? *Timothy Gardner MD, Dartmouth University*
1:15pm – 1:35pm	Role of surgery in pediatric pancreatitis in 2017 *Jaimie Nathan MD, Cincinnati Children's Hospital Medical Center*
1:35pm – 1:55pm	Pain self-management interventions for children with chronic pancreatitis *Tonya Palermo PhD, Seattle Children's Hospital*
1:55pm – 2:15pm	Panel Discussion/Questions
2:15pm – 2:30pm	Break

Module 4 - New Frontiers in Pediatric Pancreatic Research
Moderators: Flora Szabo MD and Antonio Quiros MD

2:30pm – 2:50pm	Cellular and animal models in pediatric pancreatitis *John Eisses MD, Children's Hospital of Pittsburgh at UPMC*
2:50pm – 3:10pm	Novel targets in the management of pancreatitis *Vikesh Singh MD, Johns Hopkins University Hospital*
3:10pm – 3:30pm	Power of consortia and collaboration in studying pediatric pancreatitis *Aliye Uc MD, University of Iowa Hospitals & Clinics*
3:30pm – 3:40pm	NIH support for research in pediatric pancreatitis *David Saslowsky PhD, Career Development Program Director, National Institutes of Health, NIDDK*
3:40pm – 4:00pm	Panel Discussion/Questions
4:00pm – 4:30pm	Presentation of Lunch/Breakout Sessions
4:30pm	Closing Remarks
5:00pm	Networking Reception — Milano Foyer

Why do some drugs cause pancreatitis?

Sohail Z Husain, MD

Learning Objectives

1. Characterize the impact of drugs as a risk factor for pancreatitis in children
2. Learn how to distinguish whether a drug is merely associated with pancreatitis or whether it is casual to the disease
3. Determine the mechanisms by which some drugs predispose children to pancreatitis and provide future directions for studying drug-induced pancreatitis

Drug-induced pancreatitis is a major problem in children that contributes to upwards of a fifth of all pancreatitis cases. In this talk, we will review the types of drugs associated with pancreatitis in children and their relative impact as a risk factor. Establishing causality poses a challenge in many cases. Using causality metrics and specific examples, we will go over practical methods for determining whether a drug is linked to pancreatitis in a particular patient. The mechanisms underlying drug-induced pancreatitis are a black box. The talk will end by discussing what is known about the mechanisms for some of the leading causes of drug-induced pancreatitis and future directions for research in this hot area.

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Genetics and the impact of CFTR mutations in pancreatitis

Tanja Gonska MD

Learning Objectives

1. Describe genetic causes as risk for acute recurrent and chronic pancreatitis in children
2. Define the role of CFTR mutation as risk for acute recurrent and chronic pancreatitis
3. Discuss future potential therapies in patients with CFTR-related acute recurrent and chronic pancreatitis

Genetic analysis in 220 children with acute recurrent (ARP) or chronic pancreatitis (CP), as part of a large multicentre study (INSPPIRE, PI: Aliye Uc), revealed the presence of gene mutations in 48% and 73% of the children respectively. In fact, gene mutations were the most common risk factor for the development of ARP/CP in this cohort [1]. Among the genes with proven association to ARP/CP are the trypsinogen gene (PRSS1), the serine protease inhibitor Kazal-type 1 (SPINK1), chymotrypsin C (CTRC) and the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), which are now being routinely tested in the clinical setting [2]. Interestingly, the CFTR gene accounted for 34% ARP and 23% CP of all identified gene mutations [1]. Kalydeco™ and Orkambi™ are the first drug targeting the primary molecular defect of CFTR mutations and its introduction into clinical care has revolutionized the outcome of patients with Cystic Fibrosis [3,4]. While they target very specific CFTR mutations, other drugs with a different CFTR mutation profiles are soon to follow. Having these drugs available and approved by the main Health authorities provides a unique opportunity for targeted drug treatment of ARP/CP children in whom CFTR contributes to the disease pathogenesis.

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Emerging Data: Evaluation of the Child with Pancreatitis including Endoscopy

Quin Liu MD

Learning Objectives

1. Describe the current roles of endoscopic ultrasound (EUS) and endoscopic retrograde cholangiopancreatography in the evaluation and treatment of pediatric recurrent acute and chronic pancreatitis
2. Discuss the limitations of endoscopic intervention in the treatment outcomes of both RAP and CP
3. Discuss the potential future of endoscopic elastography in the evaluation of CP

Endoscopy continues to play an important role in the evaluation and treatment of acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP). From the evolution of endoscopic retrograde cholangiopancreatography (ERCP) to the advent of endoscopic ultrasound (EUS), the pancreas can now be assessed in a much more minimally invasive way than ever before.

EUS can provide an extremely detailed visual and tissue sampling of the pancreas for diagnostic purposes while ERCP is usually reserved for therapeutic indications. This talk will discuss the various ways both EUS and ERCP can evaluate and treat different pancreatic pathology such as pancreatic fluid collections, pancreatic walled of necrosis, duct strictures, and duct stones. We will also review the efficacy and limitation of endotherapy in pediatric pancreatitis.

Implementation of new endoscopic modalities such as EUS elastography and microbubble contrast-enhanced EUS have potential to further improve our ability to characterize pancreatic diseases.

The progression from acute to chronic pancreatitis

Christopher Forsmark MD

Learning Objectives

1. Appreciate the long-term natural history of acute and acute relapsing pancreatitis
2. Understand the clinical and genetic risk factors for progression from acute to chronic pancreatitis
3. Understand the differences in progression to chronic pancreatitis in children compared to adults

While the definition of acute pancreatitis includes a complete recovery of pancreatic structure and function after an attack, a significant proportion of patients will develop exocrine or endocrine insufficiency, which may be transient. With repeated attacks, the risk of progression to chronic pancreatitis increases. The progression to chronic pancreatitis is unpredictable, but is more common in those with an initial episode of necrotizing pancreatitis, those with repeated attacks, those who smoke or drink, and those with genetic causes of pancreatitis. Preventing progression is currently not possible, although avoidance of environmental toxins is likely to slow progression.

Imaging Methods to Access Pancreas in Children

Andrew Trout MD

Learning Objectives

1. Understand the imaging modalities available for assessment of pediatric pancreatic disease.
2. Recognize when to use one imaging modality versus another for specific indications.
3. Understand advancements in imaging technology and technique that may bring value to assessment of pediatric pancreatic disease.

Optimal imaging of pediatric pancreatic diseases is disease specific but in general terms, cross sectional imaging including ultrasound, CT and MRI brings the greatest value to assessment of the pancreas. Each of these modalities has advantages and disadvantages related to cost, field of view, speed, radiation exposure and need for intravascular contrast material. This talk will review the dominant imaging modalities as they relate to assessment of pediatric pancreatic disease with attention to the increasing need for imaging related to pediatric pancreatitis, acute and chronic. Technologic and technical advancements in each of the modalities that bring added value to assessment of pediatric parenchymal disease will also be discussed.

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Do's and don'ts of endoscopic pancreatic function testing

Maisam Abu-El-Haija MD

Learning Objectives

1. Understand the differences methods, and interpretation of indirect and indirect pancreatic function testing.
2. Learn the evolution of pancreatic function methods from the early 1950s until today
3. Understand the limitations of pediatric endoscopic function testing.
4. Highlighting areas for future research.

Exocrine pancreatic insufficiency (EPI) results from different underlying etiologies and has negative implications on the children's growth and health. Congenital syndrome can lead to EPI in children amongst which are Cystic fibrosis, Shwachmann Diamond Syndrome, Pearson Marrow Syndrome, Jeune Syndrome and others. All of these present in the early years of life rather than in adulthood, making EPI mainly a pediatric problem. Regardless of the underlying etiology for EPI, it remains a condition that has serious sequelae and can lead to malabsorption, and growth failure if not promptly diagnosed and treated. Pediatric Gastroenterologists are more likely comfortable with ordering indirect pancreatic function testing (fecal elastase, 72 hour fecal fat and others) and less likely to perform direct pancreatic function test. The Dreiling method and the endoscopic function tests are what is considered the "gold standard" for EPI Dx. My talk will over this topic in a fashion that is meant to be educational for pediatric gastroenterology specialists because many are very uncomfortable with the endoscopic pancreatic function testing in children, mainly due to the limited knowledge.

Diagnosis of PEI and treatment with PERT in 2017

Mark Lowe MD

Learning Objectives

1. Describe the exocrine functions of the pancreas
2. Identify the symptoms related to maldigestion of various nutrients
3. Discuss the advantages and disadvantages of different methods to test pancreatic exocrine function
4. Understand the physiology that affects the treatment of pancreatic exocrine insufficiency
5. Be aware of new approaches in development for treating pancreatic exocrine insufficiency

The exocrine protein secretes water, bicarbonate and enzymes required for the digestion and absorption of dietary carbohydrates, protein and fat. The malabsorption of dietary fat accounts for most of the symptoms and complications of pancreatic exocrine insufficiency. Several tests are available for measuring pancreatic exocrine function. All have shortcomings. Treatment remains pancreatic enzyme replacement with extracts of animal pancreas. New approaches to treatment, including recombinant digestive enzymes, are in development.

Management of AP in adults: Which lessons are applicable to pediatric care?

Tim Gardner MD

Learning Objectives

1. Outline the changing demographic and etiologic landscape of acute and chronic pancreatitis in adults, and how this is applicable to a pediatric population
2. Describe the advanced diagnostic and management tools that are increasingly used in adults and applied to the pediatric population
3. Discuss the expanding role of TPIAT in the pediatric population

As in the adult population, the prevalence of pediatric acute pancreatitis is increasing and accompanied by changing trends in etiology. Whereas in the past decades it was believed that most causes of pediatric acute pancreatitis were due to infection, increasingly children are developing pancreatitis due to biliary disease, medication reactions and an increased recognition of idiopathic duct centric (type 2) autoimmune disease. In addition, the discovery of underlying genetic etiologies has allowed greater insight into disease prognostication both in acute and chronic pancreatitis. Tools that allow for more advanced diagnostic and management techniques such as endoscopic ultrasound and ERCP are also being used more frequently in children. Finally, the improved access to total pancreatectomy with islet cell transplant has revolutionized the means by which adults, and now children, can possibly be treated for severe recurrent acute/chronic pancreatitis

Role of Surgery in Pediatric Pancreatitis in 2017

Jaimie D. Nathan, MD

Learning Objectives

1. Describe the indications for surgical intervention for chronic pancreatitis in children.
2. Recognize the operative approach to and postoperative management of total pancreatectomy with islet autotransplantation (TPIAT) in children.
3. Describe the outcomes of TPIAT in children and the future directions in the field.

Acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) are increasingly diagnosed in the pediatric population. While most children with ARP or CP can be successfully managed medically, a subset of patients suffer from debilitating pain and markedly impaired quality of life. Surgical interventions play a role in the management of this challenging patient cohort. Conventional surgical approaches, including resections and drainage procedures, may be considered in the setting of specific morphology and anatomy of disease. However, most pediatric patients with ARP/CP lack such morphologic features, and it is in this cohort of patients that total pancreatectomy with islet autotransplantation (TPIAT) represents an important and viable option. The primary goal of TPIAT is to relieve incapacitating pain of CP or debilitation of ARP when maximal medical therapies and endoscopic approaches have failed. Total pancreatectomy removes the nidus of chronic pain and debilitation, while the goal of islet autotransplantation is to preserve endocrine function. In appropriately selected children, TPIAT achieves liberation from chronic opioid use and durable pain relief and improves quality of life with manageable glycemic control. A comprehensive multidisciplinary care team is critical to ensuring optimal outcomes following TPIAT in children.

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Pain self-management interventions for children with chronic pancreatitis

Tonya Palermo, PhD

Abdominal pain is present in the majority (81%) of pediatric patients with acute recurrent (ARP) or chronic pancreatitis (CP). Children with pain are subjected to a high number of medical investigations, surgical interventions, and opioid prescriptions. As pain becomes more frequent and severe, it reduces health-related quality of life (HRQOL) across multiple domains of physical, psychological, and social functioning. Pain also impacts healthcare utilization and is associated with a high economic and societal burden. Children with ARP/CP will continue into adulthood with pain, often with worsening disease and greater exposure to opioids. Thus, intervention during childhood presents a unique opportunity to teach effective pain self-management that may decrease emergency room visits and hospital admissions, reduce opioid use, and subsequently prevent or lessen the enormous impact of adult chronic pain and its associated disability. In other chronic painful conditions including gastrointestinal disorders, self-management interventions have been effective for reducing pain and pain impact including disability and depressive symptoms in pediatric and adult populations. Availability of information and communication technology has expanded opportunities for intervening with individuals remotely. Despite their relevance, to date, self-management interventions have not been evaluated in individuals with CP. Preliminary work to adapt an internet-delivered pain self-management intervention to treat pain and pain-associated disability in children with ARP and CP will be presented.

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Cellular and animal models in pediatric pancreatitis
John Eisses MD

Learning Objectives

1. Outline common experimental models of acute and chronic pancreatitis?
2. Discuss limitations of experimental models of pancreatitis.
3. Discuss the relevance of animal models of pancreatitis to human disease.

Pancreatitis is a life-threatening inflammatory disorder that lacks targeted therapies. It is the 3rd most common inpatient gastrointestinal diagnosis in the US[1,2]. Despite its sizeable morbidity and mortality, treatments for pancreatitis are still largely supportive. There are currently no targeted therapies. Most experimental therapeutic strategies have focused on ways to control the florid inflammation that occurs[3,4]. The challenge is that by the time most patients present with pancreatitis, marked pancreatic injury has occurred and multiple inflammatory pathways have already been activated. A major obstacle in developing preventative or therapeutic strategies has been the lack of a definitive understanding of the pathobiology of pancreatitis. In addition, the onset of pancreatitis can be triggered by several putative mechanisms that result in the injury to this retroperitoneal organ and impact the course of pancreatic recovery. Our current understanding of the pathophysiology of pancreatitis is based on animal studies due to the inaccessible nature of human pancreatic tissue. Fortunately, several animal models of acute and chronic pancreatitis have been developed and these can facilitate a deeper understanding of the pathophysiologic mechanisms that drive pancreatic injury and the recovery mechanisms that allow pancreatic regeneration[5,6,7]. An understanding of the injury mechanism and limitations of specific experimental animal models will allow appropriate choice of an experimental model to answer questions that are relevant to clinical pancreatologists. We present an introduction to several animal models for the study of acute and chronic pancreatitis.

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Novel targets in the management of pancreatitis

Vikesh Singh MD

Learning Objectives

1) Review challenges of finding target(s) to treat pancreatitis
2) Review pitfalls of prior studies evaluating pharmacologic therapies for pancreatitis
3) Review the targets of drugs that are currently under development for the treatment of pancreatitis

The pathophysiology of acute pancreatitis is complex and poorly understood. Most of our understanding of these pathophysiologic pathways are based on animal models which typically do not correlate with human disease. As a result, no single target for drug development has emerged and care of the patient with acute pancreatitis remains supportive. While many drugs have been evaluated for the treatment of acute pancreatitis, no drug has been found to be effective thus far. The limitations of these studies include small sample sizes, inclusion of patients with variables times between the onset of symptoms and presentation, lack of adjustment for co-interventions that impact outcomes (e.g. fluid therapy), lack of a common definition of severe acute pancreatitis, and most importantly, a lack of clear endpoint(s) that incorporate clinical and patient-reported outcomes. There has been significant progress in the pharmacologic prophylaxis of post-ERCP pancreatitis and in the secondary prophylaxis with the development of an antisense apoCIII inhibitor for patients with hypertriglyceridemic pancreatitis. Targets of drug development programs at the present time include the complement cascade and contact system as well as calcium signaling within acinar cells.

Power of consortia and collaboration in studying pediatric pancreatitis

Aliye Uc MD

Learning objectives

1. Understanding the epidemiology of pediatric pancreatic diseases
2. Progress in pediatric pancreatic disease research over the years
3. Opportunities to explore knowledge gaps

Pancreatic inflammatory diseases are relatively rare diseases of childhood. Acute pancreatitis affect roughly 1 in 10,000 children; 15-35% of children develop recurrent episodes, a small subset acquires chronic pancreatitis (possibly <1 in 100,000) [1]. Although alcohol and gallstones are commonly seen in adults with acute pancreatitis, etiologies in children are broad (biliary/obstructive factors, systemic illness, medications etc) and many are idiopathic. Genetic and anatomical factors are most commonly associated with pediatric acute recurrent and chronic pancreatitis [2]. Data shows that although rare, pediatric pancreatitis is costly and significantly impact children's and families' lives [3, 4].

There has been an increase in the number of children diagnosed with acute pancreatitis within the last decade, probably because of increased awareness. Most papers published in pediatric pancreatitis describe risk factors and sequela; there are only a few that focus on treatment and outcomes. For the management of childhood pancreatitis, pediatricians have long relied on adult literature or personal/institutional experiences. Societies, including NASPGHAN and ESPGHAN are now developing consensus criteria for management of pediatric pancreatitis, but these mostly rely on expert opinion or adult literature [5, 6].

Pediatric pancreatology field desperately needs evidence-based research of highest quality with double-blinded randomized controlled clinical trials and validated outcomes. Because pediatric pancreatitis is relatively rare, large numbers of patients for such studies can only be acquired through a multicenter collaboration. INSPPIRE (INternational Study Group of Pediatric Pancreatitis: In search for a cuRE) was the first ever NIH-funded multicenter pediatric study on acute recurrent and chronic pancreatitis [7]. Its role can be expanded to involve randomized controlled trials with the goal to develop better therapeutic alternatives to children with these diseases. Finally, a similar collaboration can be developed for acute pancreatitis.

Pediatric pancreatology field has come a long way within the last decade. Future priorities should include to continue our understanding of pediatric pancreatitis, develop cellular and animal models to study phenotypes, focus on pathophysiology, natural history, risk stratification and improve care for a patient-centered approach.

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