Pancreatitis Boot Camp

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Noon Conference August 12, 2020

Roadmap

- Background
  - Pathophysiology
  - Diagnostic Criteria
- Medical Management
- Endoscopic management
- Surgical Management
- Top 5

UCSF Pediatric Pancreas Program
• Launched in 2015
• Unmet need = Coordinated, expert care for children with chronic pancreatic disease
• Goal = To coordinate and elevate the multidisciplinary expertise provided at UCSF in the care of children with chronic pancreatic disease and their families

INSPPIRE: International Study Group of Pediatric Pancreatitis: In search for a cure
• Now INSPPIRE 2
• 22 sites
  • 18 U.S.
  • 2 Canadian
  • 1 Israel
  • 1 Australia

What does it do again?
Endocrine vs Exocrine

Photos from pathology.jhu.edu/pancreas
Leifsaul.com, 2018

Pancreatitis

Process of autodigestion in acute pancreatitis

Etiologic Factors
- Obstruction
- Direct toxic injury to pancreatic cells
- Production & release of pancreatic enzymes
  - Trypsin
  - Activation of other enzymes
  - Edema
  - Necrosis
  - Hemorrhage
- Lipase
- Phospholipase A
- Elastase
- Hemorrhage
- Kallikrein
- Edema
- Vascular permeability
- Smooth muscle contraction
- Vasodilation
- Shock

Pancreatitis

Pediatric Acute Pancreatitis vs Chronic Pancreatitis
Consensus from INSPPIRE Group

• Acute (in the absence of evidence of irreversible, structural changes of the pancreas)
  At least 2 of the following:
  1) Characteristic abdominal pain
  2) Imaging consistent with AP
  3) Lipase or amylase > 3x's ULN

• Chronic
  • Irreversible structural changes in the pancreas + at least 1 of the following:
    1) + consistent abd pain or lipase/amylase > 3x's ULN
    2) + EPI
    3) + endocrine pancreatic insufficiency

Pediatric Acute Pancreatitis vs Chronic Pancreatitis

Chronic pancreatitis in children and adolescents

- Rare but exists!
- Median age at first attack: 0.8 years (IQR 4.7-12.1 years)
- Painful chronic disease
- Mean 2.3 hospitalizations per child per year
- 57% report constant pain
- 12% pancreatic enzyme insufficiency
- 6% diabetes
- 18% report daily or weekly opioid use

What causes chronic pancreatitis in children?

Genetics

- Premature activation of trypsinogen
- Destruction, inhibition, or elimination of trypsin from the pancreas
- Genetically linked chronic pancreatitis linked to alterations in trypsin control

CFTR related disorder

- Clinical disease limited to only one organ system associated with some evidence of CFTR dysfunction that do not meet full genetic or functional criteria for a CF diagnosis
- Should have surveillance to assess for new manifestations of disease
- Receive genetic counseling
- Estimated prevalence and disease manifestations evolving

Obstructive

- Gallstones
- Pancreas Divisum
- Annular pancreas

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Goals of treatment

• Pain relief
• Improve daily function (participation in school, activities etc)
• Preserve pancreatic function (Exocrine & Endocrine)
• Minimize emotional affects
• Minimize trauma
• Prevent Narcotic Dependence
• Overall improvement in quality of life

Medical Management & Treatment Options for children with ARP/CP

• Pancreatic enzyme replacement—at least 15-30 mins before eating
• Pain medications (narcotic or not)
• CFTR modulators CFTR related disorder
• Celiac plexus ablation
• Non-pharmacologic treatment:
  • Endoscopic therapies

Pain

80-95% patients present with abdominal pain with AP
Only 1.6-5.6% of pediatric patients have “Classic” pain
Pathophysiology of pain in AP
Treatment of pain
**Acute pain specialist services should ideally be consulted in cases of more severe pain to optimize pain management

Frequent Opioid Use in Children with ARP/CP

• Of 427 children/adolescents with ARP or CP, 17% reported daily or weekly opioid use.
• Concurrent physician surveys on those with frequent opioid use reported opioid use less than weekly in 39% and were missing data on frequency in 18%.
• Children in the U.S. West and Midwest = 83% of children reporting frequent opioid use but only 14.5% of total cohort.

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Medical Management

Endoscopic management
Surgical Management
Top 5

Endoscopic Retrograde Cholangiopancreatography (ERCP)
What does chronic pancreatitis look like in children?

3.5yo with PRSS1 mutation, 1st pancreatitis age 2.5y

9yo with SPINK1/CFTR mutations, 1st pancreatitis at age 6y

Post-ERCP complications

- Pancreatitis** (incr. 2 → 5%)
- Infection: cholangitis, cholecystitis, sepsis
- Perforation: retroperitoneal duodenal**, biliary (Decr. 1%→0.2-0.3%)
- Bleeding: luminal or intra-peritoneal (Decr. 3%→2%)
  - Sphincterotomy**
  - Duodenal hematoma
  - Bile duct varices
  - Pseudoaneurysm
- Risk factors: sphincterotomy, difficult cannulation, stent placement

ERCPs in pediatric ARP and CP

- Therapeutic ERCP: 30% of children in INSPPIRE
- CP > ARP
- Children with obstructive factors (pancreas divisum, history of gallstones, choledochal cyst) more likely to have ERCP
- BUT, only ~20% of centers with pediatric gastroenterology in a recent nationwide survey offer ERCP for children with pancreatitis
- In INSPPIRE cohort, ERCP felt to be effectively therapeutic in 54%

How helpful is ERCP-delivered therapy in children with chronic pancreatitis?

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Not Helpful</th>
<th>Helpful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary sphincterotomy</td>
<td>45%</td>
<td>42%</td>
</tr>
<tr>
<td>Biliary stent</td>
<td>50%</td>
<td>48%</td>
</tr>
<tr>
<td>Pancreatic sphincterotomy</td>
<td>48%</td>
<td>50%</td>
</tr>
<tr>
<td>Pancreatic stone removal</td>
<td>50%</td>
<td>48%</td>
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</tbody>
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Surgical Options

What if medical and endoscopic management don't provide relief?

- Puestow - Pancreaticojejunostomy
- Whipple - Pancreaticoduodenectomy
- Distal Pancreatectomy

TPIAT (total pancreatectomy with islet auto-transplant)

UCSF = 1 of 3 pediatric centers in the U.S. that offers TPIAT

What are the goals of TPIAT?
- Provide pain relief
- Improve quality of life
- Decrease hospitalizations, increase school attendance
- Preserve islet function
- Wean from narcotics
- Decrease risk of malignancy

What do we consider TPIAT?
- Frequent hospitalizations
- Signs of chronic pancreatitis on imaging (MRI, EUS, ERCP)
- Inability to function (eg: missed school, avoidance of activities)
- Signs of islet destruction
- Lack of improvement despite medical management (eg, exogenous pancreatic enzymes) or endoscopic therapies
- Hereditary pancreatitis and risk of malignancy over time (i.e., PRSS1 mutations)

Preparing children and their families for TPIAT

Patient and Family Centered Education
- Minimum of 3 Teaching sessions
- Video visits and in person
- Pancreas NP
- Diabetes Educator
- Pancreas LMFT
- Child life Specialist
- Pain Anesthesia & Psychologist
- Post-op TPIAT “guide”
- Goal: Atraumatic Coordinated Care

Pediatric TPIAT at UCSF
- N=23 (2013)
- Age at TPIAT: median 13yo (range 4-22yo)
- 60% Female
- 80% with hereditary pancreatitis mutations
- 50% PRSS1 mutation
- Islet yield: median 7,325 IEQ/kg (1,551-14,905)
- Post-TPIAT LOS: 20 days (1yr outcomes)
- More recent average LOS is ~14 days
Challenges for patients, families, caregivers...and providers

- Lifelong burden with chronic disease (often chronic pain) + unpredictable, painful flares
- No cure
- Risk of:
  - Exocrine failure
  - Endocrine failure
  - Pancreatic CA (for some)
- Stressful/traumatic for child and family:
  - Hereditary with dominant pattern (multiple family members)
  - Impair QOL and family functioning

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Patient IB

- 6yo F abdominal pain, h/o AP x2, no pertinent family hx
  - Location: epigastric bores through to the back
  - Pain 10/10
  - Sharp, stabbing
  - Random woke up with the pain
  - +N/V, inability to take PO's

Poll #1
What labs would you want to check?

Assessment and surveillance ARP & CP

1. What labs should I check (Diagnosis vs surveillance +/- genetic)
2. What imaging should I get/should we do an ERCP?
3. Should we check/follow lipase levels?
4. Should they start exogenous pancreatic enzymes?
5. When patients call-do they need to come to the ER every time? Can I give my patient narcotics and let them self-manage at home?

How does UCSF’s Pediatric Pancreas Program help with these challenges?
**Patient IB**

- Started on R, IV + IV Pain control
- Initial labs:
  - Lipase >400 U/L (ULN = 90 U/L)
  - CRP = 10
  - AST, ALT, GGT, TBili (WNL)
  - Calcium 8
  - TG's WNL
  - HR 120's, BP's 110-120/60-70; afebrile
- Recent ABD US: Findings suggest ectatic and tortuous pancreatic duct, with possible pseudocyst formation. Moderate complex free fluid in the pelvis.

Poll #1: What kind of imaging would you order?

**INSPIRE consensus**

- Choice of imaging modality should consider & minimize radiation exposure (level 1A, definitely yes, strong consensus)
- Initial evaluation of ARP should include imaging of the pancreas (1B)
- Detailed imaging of pancreatic ducts and biliary tree (MRCP) should be undertaken acutely if GGT >2x ULN or D bilii is elevated, even in the absence of a/o obstructive etiology on US (1B)
- MRCP should be completed with ARP (ERCP/EUS may be alternatives depending on the situation) (1A)

**Imaging in Pancreatitis: Type and Timing**

- **ABD US:**
  - Gallstones/biliary
  - +/- splenic artery pseudoaneurysm; splenic thrombus
- **Contrast-enhanced CT (adults):**
  - Neurorad (first 24-48hrs vs >72hrs after symptom onset)
- **MRCP:**
  - Secretin-enhanced MRCP (opposed to standard MRCP) should be obtained to evaluate the bile ducts, pancreatic ducts
- **Evaluation of the bile ducts, pancreatic ducts (nonionizing radiation):**
  - Necrosis (first 24-48hrs vs >72hrs after symptom onset)
  - Characterize pancreatic & peripancreatic collections or abscess
- **With protocol:**
  - Evaluate ductal abnormalities
  - Detects choledocholithiasis
  - Identify duct leaks/disconnections
  - Characterize pancreatic & parenchymal collections or abscess
  - With angio: identify hemorrhage within pancreas or peripancreatic collections or pseudocysts
- **EUS:**
  - “Supersedes” MRCP
  - Helpful with assessment of microlithiasis
  - Evaluate ductal abnormalities

Pt IB: Imaging Results

- **MRCP shows:**
  - Diffuse atrophy of pancreas: extensive dilation of the pancreatic duct with multiple obstructing stones measuring up to 1.3 cm (series 401, image 38), possible due to impact of D bilii
  - ERCP: Cannulation of the PD through the major papilla was performed. Pancreatogram revealed a markedly dilated and tortuous pancreatic duct measuring 14mm in the head, filled with non-obstructing stones. There was undulating and dilated, and there were other stones throughout the duct. Pancreatic sphincterotomy was performed and yielded multiple white waxy stones and crushed fragments. A 7Fr-5cm double pigtail stent was placed in the head of the pancreas to facilitate drainage in hopes that it would prevent additional stones with respiratory movement. The remaining stones will be removed in subsequent ERCPs.

**Lipase/amylase as markers of severity**

- **Limited value for repeated amylase/lipase in management of acute pancreatic injury:**
  - Amylase/lipase lags behind clinical events; elevated for 4-7 days
  - Amylase/lipase may not be elevated in late stage pancreatitis

- **Possible role:**
  - Potential role in management of acute pancreatitis
  - May be useful in early detection of acute pancreatitis
  - May be useful in determining the severity of acute pancreatitis
  - May be useful in monitoring the response to treatment

**References:**


Biochemical markers of Pancreatitis

- Lipase
  - Other causes of increase (acute cholecystitis, biliary obstruction)
  - Abnormal results: elevated, peak at 24 hrs, decrease over 3-4 days (higher than amylase)
- Amylase (pancreatic and salivary salivary):
  - Secreted by pancreas, salivary glands, small intestine, sources, adipose tissue, skeletal muscles
  - Fluctuates 0-24 hours, peak at 48 hrs, decrease to normal over 5-7 days
- urinary trypsinogen-2
  - Similar sensitivity and specificity to serum lipase
  - One pediatric study similar findings
- Rapid urinary testing 3 hours after ERCP used to detect early Di of post ERCP pancreatitis
- With AP- rise within a few hours and decrease in 3 days
- Common threshold is 50mg/L

- Trypsin activation peptide (TAP) + urinary trypsinogen-2
  - Accurate, but not widely available
  - Early elevated urine TAP levels associated with more severe pancreatitis in adults

Pancreatic Enzyme Replacement Therapy (PERT)

- Pancreatic patients with pancreatic insufficiency need PERT to replace endogenous enzyme production
- Pancreatic patients who still have adequate pancreatic function receive PERT with meals in an attempt to decrease pancreatic stimulation
- Oral PERT: enteric-coated microspheres that dissolve at a pH of >5.5 (protects enzymes from gastric digestion)
- PERT is given with every meal and snack
  - Exception: pancreatitis patients do not need PERT with non-fat items or while on clear liquid diets
  - Proton pump inhibitors are sometimes given to improve efficacy of PERT

Dosing Guidelines PERT

- Weight Based Dosing
- Fat grams/day

Possible adjustments:
- Dose
- Brand
- Timing (eg split dose)
- Grams of fat

PERT with EN

- Order set pending

- Pain: decreased on PO narcotics and Tylenol
- Note she c/o abd pain between flare-ups
- Plan to advance her PO diet and start exogenous pancreatic enzymes (despite normal fecal elastase)

Poll:
How do I dose enzymes?
Patient IB

• Pain is controlled
• Tolerating 100% POs with PO enzymes

Poll
Should we do genetic testing?
What about sweat chloride testing?

Genetic testing - When? How? Why?

• INSPIRE consensus:
  - The search for a genetic causes of ARP or CP should include a sweat chloride test (even if newborn screen negative) and PRSS1 gene mutation testing (definitely yes, 1A)
  - SPINK1, CFTR, CTRC may identify risk factors for ARP and CP (definitely yes, 1B)

Genetic Testing
How to:

- Online account
  - Set up account with Invitae (www.invitae.com)
  - Select organization "UCSF" (Make sure it's 400 Parnassus Ave (NOT MB) to be linked to other Peds GI providers)
  - Order Invitae kits PRN (Invitae portal > Request a kit > Choose Blood Kit)

- Forms & Kit to bring to patient
  - Order requisition form (with patient information and insurance completed)
  - Patient consent: Invitae website > forms > diagnostic tests > "Panel Tests: patient informed consent" (*order provider also signs consent)
  - Invitae (or other genetic company) kit (stored in MH on cubicle outside RM 5301)

How to Order

- Log in to Invitae portal
- "Start an Order"
- "Invitae Chronic Pancreatitis Panel": CASR, CFTR, CTRC, PRSS1, SPINK1, CPA1
- Complete ordering fields (patient name, demographics, insurance found in APEX)
- Select self as ordering provider (or select ordering provider who has authorized the test)
- "Order Authorization page": select "I do not have my patient's email"
- Select "by signing this form ..." enter your initials in the box at the bottom
- Select "Complete Order" to submit
- Print requisition form for ordering provider to sign
- Print patient consent form (input "Pancreatitis" in item #1 "condition tested"

In-person work - flow

- Bring complete requisition and blood collection kit to clinic/hospital visit
- Bring patient consent form (needs to be signed by ordering provider and patient/parent; parent signs if patient <18yo)
- Order provider to order labs for patient
- If in hospital, can use "Misc Outside Lab, #271991286" and enter nursing note to KEEP TUBE AT BEDSIDE for pickup (do NOT SEND TO LAB)
- MA/RN to accompany patient/family to lab and ask phlebotomist to draw an additional 6-cc EDTA purple top (provided in genetic testing kit)
- Blood sample, signed consent and signed requisition form in prepaid Fedex envelope may be dropped off at Peds Infusion center lab window (they have a Fedex pickup)

View Completed & Pending Orders

- Login to Invitae
- "Your orders & reports"
- Download report and email to Badam to upload to patient chart in APEX

**APEX Message to Christine K & cc Michelle

Patient IB

• 1 week later parent called and she's having abdominal pain and isn't eating well.

Poll
Does she need to come to the ER or can we give pain medications over the phone and have her manage at home?

Thank you
Research

Prospective, observational cohort study of children with acute recurrent and chronic pancreatitis

Genotyping of all children

Biobanking of longitudinal samples

Risk factors for progression to chronic pancreatitis, exocrine and endocrine insufficiency in a prospective study (PERITO)

INSPPIRE 2:

What fluids do I use?

• Fluid replacement & optimization of electrolyte balance
• Replace tissue lossing, decreased POs, total output, fifth fluid 1000 mL/h IV
• Therapeutic interventional window: 3-5 days
• Hypo or Hyperglycemia
• Anticoagulation
• pTT goal: vary by patient, usually 50-60

Acute post-op monitoring

• Intraoperative complications
• Post op:
  - Hospitalized average 14 days here at UC
  - Post op mortality rates low (<2%) in one case review
• Most complications:
  - UTI (17%)
  - Catheter related bacteremias (12.5%)
  - PNA (12.5%)

Acute post-op management

• Glucose management and insulin
  - Insulin gtt → long/short-acting
  - Carb correction when taking PO's
  - Goal: providing exogenous insulin to suppress islet function and allow islets a chance to engraft.
  - Goal blood glucose 80-130 (gtt); 70-120 (insulin pump)

Pediatric TPIAT at UCSF: 1 year later

• N = 15
  - 80% off opioids
  - N=3 had been weaned but re-started at 1 year still required less than at discharge post TPIAT
  - 33% insulin independent
  - Those on insulin required low doses
  - Almost 2/3 had 0-1 visit to the ED
  - 3 of those who required hospitalization 2-3 times were on opioids at 1 year

Higher islet yield correlated with lower insulin dose at 1 year

Acute Post-TPIAT common concerns:

• Bleeding
  - Monitoring
    - Vitals: hypotension, tachycardia
    - JP drain, GJ tube: increased bloody output
    - CBC q 4 first 48 hours: drop in Hct

• Hypo- or Hyper-glycemia
• Insulin algorithm
• Anticoagulation

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Acute post operative management

- Infection (islet cultures, splenectomy ppx)
- Anti-coagulation (risk of PV thrombosis)
  - Heparin gtt x ~48 hours → Lovenox x 2 wks
  - Ultrasound on POD1/PRN for flow in portal vein
  - Arterial line
- Pain management: usually PCA
  - Most patients have pain team involved, many are opioid naive
  - Non-pharmacologic modalities

Post-operative management

- Ileus/Gastroparesis:
- EPI/Diarrhea vs. constipation
- Splenectomy (IMZ, ABX, thrombocytosis)
- Pain
- Insulin Dependence
- Psychological (PTSD?)
- Expectations
- Nutrition
  - GJ tube
  - Enteral feeds if needed, POD 3-4
  - Pancreatic enzyme replacement (enzymes mixed with feeds)
  - Advancing PO...
  - Nutrient/Vitamin deficiency
  - Wound healing

Addition of Pancreatic Enzymes with Enteral Feeding

- Crush the VioKace tablets
- Mix with a 4 hour volume of formula in the tube feed bag.
- Allow the VioKace and formula to sit for 15-20min to allow for pre-digestion of the formula prior to infusion.
- Gently agitate contents as formula breaks down
- Flush J tube port q 4 with 10-20 ml warm water to ensure patency.

Tools

- Continuous Glucose Monitor
  - Reasonable accuracy after calibration
  - Requires frequent calibration (up to Q3 hrs)
  - False readings with acetaminophen and thrombocytosis (generation dependent)
- Insulin Pump vs Injection
  - Transition from insulin gtt→pump & decreased PICU LOS?

ARP & CP as initial presentation of CF & CFTR-related disorders

- UCSF/UT Southwestern case series
- N=18 patients
- Diagnosis:
  - N=8 Elevated sweat chloride
  - N=5 Intermediate sweat chloride (30-59 mmol/L) + 2 pathogenic mutations
  - N=5 >0-1 mutations
- 44% EPI at Dx
- 28% Diabetes/Prediabetes at diagnosis
- N=6 pt’s eligible for CFTR potentiator therapy (based on CFTR mutations)
- 9/18 had ≥2 other likely CF manifestation:
  - 33% Sinusitis, 11% nasal polyps, 22% PNA, 22% Gallbladder dx
- Only 1 pt with FEV1% <80%

UCSF Experience with CFTR modulators in ARP/CP with CF mutations

- N=3 patients with CP + CF mutations + positive sweat chloride or nasal impedance testing
  - Chronic lipase elevation + Pain
    - 1 resolved
    - 1 no resolution (D/C’d CFTR modulator)
  - Chronic pain, intermittent lipase elevation
    - No significant improvement in chronic pain
  - Changed from ivacaftor → lumacaftor/ivacaftor (Orkambi) → Symdeko
CFTR modulators in ARP/CP with CF Mutations—the literature

- 1 published case series JPGN 2018
- 7/2018 AJG Case report 48yo with ARP (found to have compound heterozygous mutation G551D-R347H (Class III), FE-1 = 143 ug/g of stool) Ivacaftor (Kalydeco) had improved FE-1 6 mos later (236 ug/g) along with no return of pancaretitis attacks

- Adult scales
  - Acute physiology and chronic health evaluation (APACHE) II
  - Randson
  - CT severity index (CTSI)
  - Bedside index