What’s New in the Evaluation and Treatment of Chronic Pancreatitis?

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Learning Objectives

• 1. Review of Diagnosis of Pediatric Chronic Pancreatitis (CP)
• 2. Management Options for Pediatric CP
• 3. Emerging Trends, Targets, and Improvements in the Diagnosis and Management of CP

Features of Chronic Pancreatitis

• Progressive inflammatory disease characterized by irreversible structural changes
• Structural changes include:
  – irregular sclerosis; focal or diffuse tissue destruction
  – acinar cell +/- islet cell loss
  – inflammatory cell infiltrates
  – pancreatic duct abnormalities and obstruction
• Can result in irreversible exocrine and/ or endocrine insufficiency

1. Evaluation for Diagnosis of Chronic Pancreatitis

Overview:
How are we currently diagnosing CP?

CP: Patient Assessment

• Symptoms, QOL
  – Pain: location, type, frequency, severity
  – Eating, stooling, daily activities
• Physical Examination
  – Nutritional status? masses, tenderness
• Blood, Stool Testing
  – Fecal elastase, vitamins, biochemistry
  – Glucose tolerance test, HgbA1c
  – Functional tests – specialized centers
CP: Imaging

- Transabdominal Ultrasound
- “Pancreatic Protocol” CT
- MRI/ MRCP
  - Recent publications with secretin: Sugita R AJR 2014; Takahashi AJR 2014; Rustagi T Pancreas 2014; Sandrasegaran K Abdom Imaging 2014; Sherman S Gastro 2014
- Endoscopic Ultrasound
- ERCP

Search for Causes/ Etiologies CP

- “TIGAR-O” Classification in Adults (Whitcomb 2001)
  - Toxic; Idiopathic; Genetic; Autoimmune; Recurrent and severe acute pancreatitis-associated; Obstructive
- Retrospective Pediatric series:
  - Idiopathic, Traumatic, Biliary including Congenital Malformations, Medication-related, Hereditary-Genetic, Metabolic, Other

Diagnosis Pediatric Chronic Pancreatitis
(Clinical + Radiologic +/- Histology)

CP clinical diagnosis via one of the following 3 situations:

A. Abdominal Pain c/w pancreatic origin AND imaging findings suggestive of chronic pancreas damage
B. Pancreatic Exocrine Insufficiency AND suggestive pancreatic Imaging findings (careful- CF)
C. Pancreatic Endocrine Insufficiency AND suggestive pancreatic Imaging findings

- CP may be dx via compatible Histopathology (surgical resection, core Bx)
- Imaging modalities including CT, MRI/ MRCP; ERCP; transabdo U/S, EUS

(INSPIRE Definitions of pediatric pancreatitis. Morinville VD and Husain SZ et al; JPGN 2012 )

Genetics and Pancreatitis:
The trypsin-dependent pathologic model of chronic pancreatitis

PRSS1, SPINK1, CFTR

AIR= acute inflammatory response (acute phase protein expression)

Pain Management:
Traditional “Stepwise” Approach

- Stopping toxins; small meals and supplements
- +/- Pancreatic enzyme supplements, acid suppression
- +/- Antioxidants? (negative: Gastro 2012 ANTICIPATE)
- Analgesics: acetaminophen, NSAIDS; narcotics, centrally-acting agents (“neuropathic”), celiac nerve blocks
- Endoscopic therapies: decompression, stones, stents
- Surgical options: decompression, resections

Dilemma: When do you become more aggressive? vs Q. Harm of waiting “too long”?

2. Management Options for CP:
What have we been doing?

PAIN #1 symptom affecting QOL

Issues of exocrine, endocrine Insufficiency

Managing Complications: stones, pseudocysts

Medical  Endoscopic  Surgical
**Surgical Interventions: For Pain, Complications**

- **Types:**
  - Decompression: procedures for dilated PD
  - Resections: of affected portion of pancreas
  - Denervation: procedures: e.g. splanchicectomy

- **Timing of surgery controversial:**
  - Q. Does early surgery prevent progression of disease and reduce need for long-term opioid use, or loss of endocrine and exocrine pancreatic function?
  - But: irreversible, complications

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**Total Pancreatectomy-Islet AutoTransplantation (TP-IAT)**

- **Rationale TP:** Removing all offending tissue to eliminate pancreatitis, inflammation, pain, cancer risk
- **Rationale IAT:** To preserve islet cells to protect patient from brittle type 3c diabetes
- **Concerns:**
  - Irreversible; surgical complications
  - Pain relief not always experienced
  - Diabetes protection variable; need pancreatic enzymes
  - “Exchanging one chronic disease for another”

→ Specialized centers, criteria

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**Recent Publications: Nutrition/Medical**

  - Multicenter, prospective; non-random, non-control; low fat AA
  - \(\checkmark\) pain reduction, \(\checkmark\) improved nutritional indices

- **ENZYMES:** Pancreatic Enzymes Replacement Therapy in Patients With Exocrine Pancreatic Insufficiency Due to Chronic Pancreatitis: A 1-Year Disease Management Study on Symptom Control and Quality of Life. D’Haese JC et al. Pancreas 2014 (Online).
  - 294 CP and EP; cohort 1 (already on enzymes) or cohort 2 (not yet on)
  → Improved symptoms and QOL in both groups at 1y

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**Recent Publications: Pain Targets**

- **Pregabalin reduces pain in patients with chronic pancreatitis in a randomized, controlled trial.** Olsen SS et al. Gastroenterology 2011.
  - CP: resembles neuropathic pain; 3w; random, double-blind, placebo; 64
  - Pregabalin group → more effective pain relief, improved health status

  - Meta-analysis: 8 studies/573 pts; antioxidant vs placebo; pain
  - Antioxidants: ↑ pain relief and ↓ need for analgesics; “may be advocated as one medical therapy” for CP

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**Recent Publications: Are Earlier Interventions Better?**

- **Endoscopic Management of Early-Stage Chronic Pancreatitis Based on M-ANNHEIM Classification System: A Prospective Study.** He YX et al. Pancreas 2014 (Epub).
  - China; MRCP and CT. M-ANNHEIM staging. improved pain scores at 24m
  - Better imaging → earlier Dx. Earlier tx → improved pain, outcomes

  - 1950 to Jan 2014: Early surgery associated with ↑ complete postoperative pain relief, ↓ pancreatic insufficiency and low re-intervention rates
Recent Publications: Longer-Term Outcomes of Surgeries

  — 74; random to Beger and Frey. Ptx Q. to evaluate long-term survival, QOL, pain, exocrine and endocrine function. Results: No signif diff 16y post
    — 64; random to PD and Frey: both providing good/ permanent pain relief; QOL and survival better after Frey after 15y

Recent Publications: ERCP for Pediatric CP

  — 180 ERCP (range 1-4) in 143 kids; 13.7yo +/- 3.1 (range 5-18)
    — F/u 64% no pain; 22% improved pain; 2 → surgical drainage
    → ERCP safe therapeutic option for pancreatic disorders in children in centers with expertise; AE rates comparable to adults

• Efficiency of Pancreatic Duct (PD) Stenting Therapy in Children with Chronic Pancreatitis. G Oene et al. GIE 2014 (online)
  — 223 PD stents/ 72 kids; esp. hered pancreatitis and PD anatomic abN
    — 1# pancreatitis/y: from 1.75 to 0.23. 10 → surgery.
    → ERCP PD stents feasible, safe, effective in CP children

Publications: Pediatric TP-IAT

• Quality of Life Improves for Pediatric Patients After Total Pancreatectomy and Islet Autotransplantation for Chronic Pancreatitis. Bellin MD et al. Clinical Gastro Hepatol 2011.
  — 19 pat (5-18y) TP-IAT, 2006-2009, Minnesota; severe CP and pain; SF-36 Health Q. pre- and post- surgery; insulin needs
  — Prior surgical drainage → ↓ islet yield, ↑ insulin dependence
    → By 1y post, TP-IAT leading to improved QOL; > 60% insulin-independent or minimal insulin needs

Recent Publications: Pediatric TP-IAT Longer-Term Outcomes

  — 484 TP-IAT from 1977-2012; Minnesota; 80 HGP
  — Post TP-IAT: 90% pancreatitis pain free, sustained pain relief, > 65% partial or full beta-cell function. Improved QOL. Up to 10y fup
    → Pts with painful CP due to HGP... high lifetime risk of pancreatic cancer... should be considered earlier for TP-IAT before...
    inflammation results in ↑ pancreatic fibrosis and ↓ islet cell function

3. Emerging Trends, Targets, and Improvements in CP Diagnosis and Management

How can we Improve what we Do and what we Could do?

Trends in Diagnosis and Management: Guidelines

  — U/S 1st-line imaging CP; MRCP after secretin 2nd step
  — Pediatricians be aware of CP in DXs chronic abdominal pain
  — Attempt to determine etiology: contributory genetic etiology esp. CFTR, SPINK, PRSS, “CTRUC only recently screened”
  — Management conservative; ERCP for strictures and stones
Trends in Diagnosis and Management: Further Understanding of Genetics

• CFTR, SPINK1, CTRC and PRSS1 variants in chronic pancreatitis: is the role of mutated CFTR overestimated? Rosendahl J et al, Gut 2013.

• Variants in CPA1 are strongly associated with early-onset chronic pancreatitis. Witt H et al. Nat Genet 2013. CPA1 = carboxypeptidase A1

• Mechanisms of CFTR functional variants that impair regulated bicarbonate permeation and increase risk for pancreatitis but not for cystic fibrosis. LaRusch J et al. PLOS Genetics 2014.

Trends: Early Surgery vs Step-up? Providing Evidence for What To Do

  – CP management: conservative step-up; “burn-out” hypothesis
  – But new evidence: prolonged periods pain → peripheral and central nerve sensitization → self-perpetuating pain state
  – Thus Plan → Randomized, controlled, parallel, multicenter trial to see if early surgical intervention will benefit in terms of better pain control and preservation of pancreatic function

Trends: TP-IAT Guidelines

• Total pancreatectomy and islet autotransplantation in chronic pancreatitis: Recommendations from PancreasFest. Bellin MD et al, for the PancreasFest Recommendation Conference Participants. Pancreatology 2014.
  – Rationale: Lack of clear guidance on TP-IAT
  – 5 major areas req clinical evaluation and management addressed:
    1. Indications for TPAIT
    2. Contraindications
    3. Optimizing timing of procedure
    4. Need for multi-disciplinary team and roles of members
    5. Life-long management of issues following TPIAT including diabetes monitoring and nutrition evaluation

Future Targets? Immune-based Therapy

  – Pancreatic stellate cells (PSC) → synthesis, degradation of extracellular matrix proteins; activated PSC in CP
  – Macrophages, mast, CD4+,CD8+ T-cells implicated PSC activ’n
  →Inhibiting PSC activation ... Q. prevent panc inflammation and fibrosis?

  – Wnt signaling may mediate profibrotic effect of PSC activation → Wnt2/Dkk-1 potential therapeutic targets for CP?
Future Targets?

The NEW ENGLAND JOURNAL OF MEDICINE
November 3, 2011
Vol. 365, No. 18
A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation
Ronnie M. Khariton, M.D., Jane Dennis, M.D., M.B., Ch.B., N. Gerard McEvoy, M.D., Elizabeth Sullivan, M.D., Scott C. Bihrlie, M.D., G. Mead, B.E., M.D., Matthias Briatt, M.D., Edward F. McCauley, M.D., and D.C. Whitcomb, M.D.

Targets: CFTR Potentiation

• G551D missense mutation: affects function of CFTR channels at cell surface

• Ivacaftor (VX-770) increases time that activated CFTR channels at cell surface remain open (“potentiator”) ➔ ↑ chloride transport activity

• Study: Improved FEV1/ lung function, weight gain; decreased pulm exacerbations

• Improved sweat Cl- testing:

What about Use in Pancreatitis?

Q. CAN WE “CORRECT” or at least IMPROVE FUNCTIONALITY of mutated proteins esp. CFTR?

Summary: What is New in Diagnosis and Treatment of Pediatric CP?

• Diagnosis: Definitions, Status, Imaging
• Genetic factors: +++ Present in CP
• Multi-center Databases ➔ Better descriptions of patients, disease burden
• Therapies: More pediatric experience; globalization; more objective evaluations of timing and efficacy of interventions

Summary: Pediatric Chronic Pancreatitis

The Future

• Improved Care: more Individualized Therapy
• Pediatric Experience rather than Extrapolation
• Multi-Center Prospective Trials
• Evidence-Based Interventions

• New and Future Targets: Immune Response/ anti-fibrosis; Potentiators for genetic defects

Thank you