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

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I have no conflicts of interest to disclose regarding this presentation

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

1. Evaluation for Diagnosis of Chronic Pancreatitis

Overview:
How are we currently diagnosing 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**

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**

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

CP clinical diagnosis via one of the following 3 situations:

- Abdominal Pain c/w pancreatic origin AND Imaging findings suggestive of chronic pancreas damage
- Pancreatic Exocrine Insufficiency AND suggestive pancreatic Imaging findings (careful- CF)
- 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)

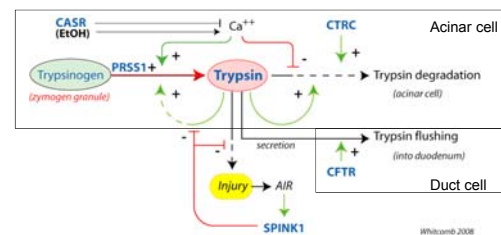
(INSPPIRE Definitions of pediatric pancreatitis. Morinville VD and Husain SZ et al; JPGN 2012)

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

Genetics and Pancreatitis:

The trypsin-dependent pathologic model of chronic pancreatitis



**PRSS1, SPINK1, CFTR
CTRC**

AIR= acute inflammatory response (acute phase protein expression)
Slide courtesy of Dr. DC Whitcomb; certain data from Whitcomb DC. *Annu Rev Med.* 2010;61:413-24.

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

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”?**

Surgical Interventions: For Pain, Complications

- **Types:**
 - **Decompression** procedures for dilated PD
 - **Resections** of affected portion of pancreas
 - **Denervation** procedures: ie splanchnicectomy
- **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

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

How are we trying to Improve Management?

Recent Publications

Recent Publications: Nutrition/ Medical

- **DIET:** Effects of Oral Ingestion of the Elemental Diet in Patients with Painful Chronic Pancreatitis in the Real-Life Setting in Japan. Kataoka K et al. Pancreas 2014.
 - Multicenter, prospective; non-random, noncontrol; low fat AA
 - ✓ pain reduction, ✓ 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 JG et al. Pancreas 2014 (Online).
 - 294 CP and EPI; cohort 1 (already on enzymes) or cohort 2 (not yet on)
 - Improved symptoms and QOL in both groups at 1y

Recent Publications: Pain Targets

- **Pregabalin** reduces pain in patients with chronic pancreatitis in a randomized, controlled trial. Olesen SS et al. Gastroenterology 2011.
 - CP: resembles neuropathic pain; 3w; random, double-blind, placebo; 64
 - Pregabalin group → more effective pain relief, improved health status
- **Antioxidant** therapy for patients with chronic pancreatitis: A systematic review and meta-analysis. Zhou D et al. Clin Nutr 2014 (epub)
 - Meta-analysis: 8 studies/573 pxts; antioxidant vs placebo; pain
 - Antioxidants: ↑ pain relief and ↓ need for analgesics; “may be advocated as one medical therapy” for CP

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
- **Systematic Review of Early Surgery for Chronic Pancreatitis: Impact on Pain, Pancreatic Function, and Re-intervention.** Yang CJ et al. J Gastrointest Surg 2014 (Epub).
 - 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

- **Beger and Frey Procedures for Treatment of Chronic Pancreatitis: Comparison of Outcomes at 16-Year Follow-Up.** J Am Coll Surg 2014 (Epub)
 - 74; random to Beger and Frey. Pxt Q. to evaluate long-term survival, QOL, pain, exocrine and endocrine function. Results: No signif diff 16y post
- **Is the Whipple procedure harmful for long-term outcome in treatment of chronic pancreatitis? 15-years follow-up comparing the outcome after pylorus-preserving pancreatoduodenectomy and Frey procedure in chronic pancreatitis.** Bachmann K et al. Ann Surg 2013.
 - 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

- **ERCP in the Management of Pancreatic Diseases in Children.** Agarwal J et al. GIE 2014.
 - 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 Oracz et al, GIE 2014 (online)
 - 223 PD stents/ 72 kids; esp. hered pancreatitis and PD anatomic abN
 - ↓ # 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 pxt (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

- **Long-Term Outcomes of Total Pancreatectomy and Islet Auto Transplantation for Hereditary/ Genetic Pancreatitis.** Srinath Chinnakotla et al. J Am Coll Surg 2014.
 - 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
 - **Pxts 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

- **Belgian consensus on chronic pancreatitis in adults and children: Statements on diagnosis and nutritional, medical, and surgical treatment.** Delhaye M et al; Acta Gastro-Enterologica Belgica 2014.
 - U/S 1st-line imaging CP; MRCP after secretin 2nd step
 - Pediatricians be aware of CP in DDx chronic abdominal pain
 - Attempt to determine etiology: contributory genetic etiology esp. CFTR, SPINK, PRSS1; "CTRC only recently screened"
 - Management conservative; ERCP for strictures and stones

Trends in Diagnosis and Management: Further Understanding of Genetics

- **CFTR, SPINK1, CTSC 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 in Studying CP: Multicenter Consortium

- **INSPIRE Consortium** (Description: Morinville and Lowe et al, JPGN 2014)

CP patients with history of ≥1 episode acute pancreatitis **	n (%)	Treatment modalities	n (%) tried
Risk factors for pancreatitis	73 (96%)	Medications (n=42)	
Genetic	51 (67%)	Pancreatic enzymes (for pain or recurrent pancreatitis)	47 (75%)
SPINK1	33 (43%)	Anti-oxidant/vitamins	14 (22%)
CFTR	11 (14%)	Steroids for autoimmune pancreatitis	3 (5%)
CTSC	2 (3%)	Oxycodone	2 (3%)
Autosomal	9 (12%)	Procedures (n=16)	
Obstructive	25 (33%)	Any ERCP	55 (72%)
Pancreas division	15 (20%)	Pancreatic sphincterotomy	45 (59%)
Subtotal of CBD dysfunction	1 (1%)	Biliary sphincterotomy	21 (28%)
Cholelithiasis	3 (4%)	Pancreatic stent	35 (46%)
Pancreatic duct malunion	2 (3%)	Biliary stent	4 (5%)
Pancreatic duct obstruction	1 (1%)	Stone removal	19 (25%)
Other	5 (7%)	Celiac plexus block	3 (4%)
Toxic/metabolic	8 (11%)	Surgery (n=14)	
Alcohol (AC, unknown)	1 (1%)	Cholecystectomy	15 (20%)
Alcohol (strongly associated)	3 (4%)	Lateral pancreatectomy	11 (14%)
Hypertension	1 (1%)	Partial pancreatectomy	1 (1%)
Metabolic disease	1 (1%)	Total pancreatectomy + islet autotransplant	21 (28%)
Other	1 (1%)		
None cited	8 (11%)		

CP Database Sept 2012- Aug 2013: Etiologies; Treatments

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

- **Early surgery versus optimal current step-up practice for chronic pancreatitis (ESCAPE): design and rationale of a randomized trial.** Ali, Usama Ahmed et al. for the Dutch Pancreatitis Study Group. BMC Gastroenterology 2013.
 - CP management: conservative step-up; “burn-out” hypothesis
 - But now 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-AIT**
 - 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 TPAIT including diabetes monitoring and nutrition evaluation

Disease burden (number of respondents)	n (%)
Patterns of abdominal pain (59)	
Usually pain free, with episodes of mild to moderate pain	10 (17%)
Usually pain free, with episodes of severe pain	21 (36%)
Constant mild to moderate pain	2 (3%)
Constant mild to moderate pain, plus episodes of severe pain	22 (37%)
Constant severe pain	4 (7%)
Mean pain scores (scale 0-100)	median (IQ range)
Constant pain (15)	65 (30-78)
Episodic pain (50)	40 (22-94)
Number of	median (IQ range)
ER visits lifelong (48)	5 (3-14)
ER visits last year (47)	3 (1-5)
Hospitalizations lifelong (52)	5.5 (2.5-14.5)
Hospitalizations last year (48)	2 (1-3)
Days of school missed past 1 month (47)	3 (0-8)
*Pancreatic insufficiency (55)	n (%)
Exocrine insufficient	19 (34%)
Endocrine insufficient	1 (1%)

Trends in Studying CP: Prospective Studies?

**INSPIRE Database
Sept 1, 2012 - Aug 31, 2013**

**Disease Burden:
Pain and Insufficiencies**

→ To help Study QOL,
Natural History

Future Targets? Immune-based Therapy

- **Immune cells and immune-based therapy in pancreatitis.** Xue J et al. Immunol Res 2014; 58: 378-386.
 - 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?**
- **Imbalance of wnt/dkk negative feedback promotes persistent activation of pancreatic stellate cells in chronic pancreatitis.** Hu Y. PLoS One 2014; 9(4): e95145
 - 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

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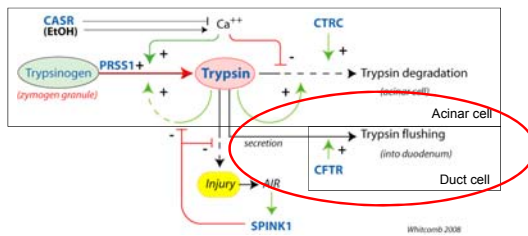
A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation

Bonnie W. Ramsey, M.D., Jane Davies, M.D., M.B., Ch.B., N. Gerard McEvoy, M.D., Elizabeth Tullis, M.D., Scott C. Bell, M.B., B.S., M.D., Pavel Dřevinský, M.D., Matthias Griesse, M.D., Edward F. McKone, M.D., Claire E. Wainwright, M.D., M.B., B.S., Michael W. Konstan, M.D., Richard Moss, M.D., Felix Ratjen, M.D., Ph.D., Isabelle Sermet-Gaudelus, M.D., Ph.D., Steven M. Rowe, M.D., M.S.P.H., Qunming Dong, Ph.D., Sally Rodriguez, M.S., Karl Yen, M.D., Claudia Ordoñez, M.D., and J. Stuart Elborn, M.D., for the VX08-770-102 Study Group*

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?

[Slide courtesy of Dr. DC Whitcomb; certain data from Whitcomb DC. Annu Rev Med. 2010;61:413-24.](#)

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