Pancreatic Cysts: Medical and Endoscopic Management

Massimo Raimondo, MD
Mayo Clinic Florida

Objectives
• Background
• Epidemiology
• Diagnosis
• Guidelines strategies
  • Observation
  • EUS-guided ablation
• Take home points
Massimo Raimondo, MD, FACG

Pancreatic Cysts: Medical & Endoscopic Management

- Non inflammatory cystic lesions
  - Small cysts found in ~½ of 300 patients*
    - 3.4% of cysts showed epithelial atypia
  - Incidentally found on
    - CT scan 2.6%**
    - MRI scan 2.4%***-13.5%****
  - Prevalence ↑ with age

**Am J Roentgenol 2008; 191: 802-7
***CGH 2010;5:806-11
****Am J Gastroenterol 2010; 105:2079-84

Pancreatic Cysts: Medical & Endoscopic Management

Increased trend of incidental cysts diagnosed over a decade by MRI

Moris, Bridges, Pooley, Raimondo, Woodward, Stauffer, Asbun, Wallace. Advances in high resolution cross section imaging and the rising prevalence of pancreatic cysts over the past decade. CGH In Press
Cystic tumors account for 1-2% of pancreatic neoplasms
- Serous cystadenoma
- Mucinous cystic neoplasms (MCN)
- Intraductal papillary mucinous neoplasm (IPMN)
  - Ductal adenocarcinoma
  - Neuroendocrine tumor
  - Acinar cell cystadenocarcinoma
  - Metastasis (ovarian carcinoma)
  - Lymphangioma
  - Sarcoma
Patients presenting with
  • M-IPMN
  • MCN
  • Cystic neuroendocrine tumors
  • Solid pseudopapillary neoplasms

Regardless of symptoms should be considered for surgery
Not discussed in this talk
Case presentation

69-yr-old WM
- Identical twin diagnosed with metastatic pancreatic cancer
- Asymptomatic
- Screening CT/MRI show 1 cm hypodense lesion, uncinate process
- PMHx: CAD with angioplasty

Pancreatic Cysts: Medical & Endoscopic Management
Factors Affecting Decision Making

- Age
- Symptoms
- Patient's preference
- Comorbidities

- Size
- Imaging morphology
- FNA results
Factors Affecting Decision Making
- Age
- Symptoms
- Patient’s preference
- Comorbidities
- Size
- Imaging morphology
- FNA results

? Natural history

Factors Affecting Decision Making
- Age
- Symptoms
- Patient’s preference
- Comorbidities
- Size
- Imaging morphology
- FNA results

? Natural history
- Surgical mortality & morbidity
Factors Affecting Decision Making

- Age
- Symptoms
- Patient’s preference
- Comorbidities
- Size
- Imaging morphology
- FNA results
- Natural history
- Surgical mortality & morbidity
- Long term complications
  - Exocrine insufficiency
  - Diabetes

Pancreatic Cysts: Medical & Endoscopic Management

**Guidelines suggest**

- Surgery should be offered to surgical candidates with
  - M-IPMN
  - Br-IPMN > 3 cm
  - Br-IPMN < 3 cm with symptoms
- Non surgical management for
  - Br-IPMN < 3 cm with no symptoms or mural nodules

Pancreatic Cysts: Medical & Endoscopic Management

**Updated Guidelines suggest**
- Surgery should be offered to surgical candidates with
  - M-IPMN
  - MCN
- Non surgical management for
  - Br-IPMN (including >3 cm) without
    - “Worrisome features”
    - “High-risk stigmata”


---

**AGA guidelines suggest**
- Cysts <3 cm without a solid component or a dilated pancreatic duct undergo MRI for surveillance in 1 year and then every 2 years for a total of 5 years if there is no change in size or characteristics

*Gastroenterology 2015; 148:819–22*
Can EUS accurately identify mural nodules?

- 11 endosonographers blindly reviewed videos before & after education regarding features
- 22 of 57 patients had mural nodules
- After education, diagnostic accuracy improved from 57→79% (p=0.004)
  - Most echogenic lesions detected in cysts by EUS are mucous
  - Knowledge of features that discriminate mucous from mural nodules improves EUS accuracy

Pancreatic Cysts: Medical & Endoscopic Management

Interobserver agreement in the assessment of malignant imaging features of IPMNs on MDCT

- Pancreatic protocol CT
  - 84 patients with resected IPMNs
  - Agreement was fair to moderate for the detection of the presence of
    - Mural nodule (κ = 0.284) or
    - Solid component (κ = 0.405)

Do, Katz, Gollub, Li, LaFemina, Zabor, Moskowitz, Klimstra, Allen. Interobserver Agreement for Detection of Malignant Features of IPMNs of the Pancreas on MDCT. AJR 2014;203: 973-9

Pancreatic Cysts: Medical & Endoscopic Management

- Retrospective review of 330 incidental CPNs
  - Correct dx of Br-IPMN 64% (32/50)
  - Correct dx of mucinous cysts 60% (18/30)
  - Correct dx of M-IPMN 94% (11/12)
  - Correct dx of SCA 91% (11/12)
  - Overall correct diagnosis 68%

Correa et al. Pancreatology 2010;10:144-150
Pancreatic Cysts: Medical & Endoscopic Management

EUS guided confocal of pancreas cysts

- Feasibility porcine study for in vivo histology


Pancreatic Cysts: Medical & Endoscopic Management

- EUS guided confocal of pancreas cysts
  - Feasibility human study (3 Institutions, 18 pts)
  - Data obtained in 17/18 pts
    - Good images obtained in 10/17 pts
    - Challenging in 6/18 pts
      - Position of the probe
      - Transduodenal approach
    - 2 cases of pancreatitis

EUS guided confocal of pancreas cysts

- Superficial vascular network pattern on nCLE with dense and subepithelial capillary vascularization only seen in SCA
  - Accuracy 87%
  - Sensitivity 69%
  - Specificity 100%
  - Positive predictive value 100%
  - Negative predictive value 82%
  - Interobserver agreement $\kappa = 0.77$

Pancreatic Cysts: Medical & Endoscopic Management

EUS guided confocal of pancreas cysts
- 15 de-identified nCLE video clips of PCLs
- 6 interventional endoscopists
- 5 institutions
- 6 variables: presence of vessels, villi, dark clumps, reticular pattern, acinar cells pattern and debris
- Interobserver agreement ranged from “poor” to “fair”: $k=0.04-0.22$
- Need to identify and validate imaging criteria to determine whether nCLE has diagnostic value for pancreatic pathology


Pancreatic Cysts: Medical & Endoscopic Management

Cystic fluid markers
- CEA
  - **Discriminates** serous from mucinous cysts
  - **Does not** discriminate benign from malignant
- MUCAC5
  - Discriminates serous from mucinous cysts
- Plectin-1
  - Discriminates benign from malignant IPMNs

Cao et al. Specific glycoforms of MUC5AC & endorepellin accurately distinguish mucinous from nonmucinous pancreatic cysts. Mol Cell Proteomics 2012
Pancreatic Cysts: Medical & Endoscopic Management

Cystic fluid markers
  - DNA based analysis
    - Mean allelic loss of amplitude/k-ras
      - Failed to indicate presence of invasive ca.
    - GNAS (codon 201)
      - Mutated in 2/3 of IPMNs (juice & cyst fluid)
      - Absent in SCA and MCN
      - Does not predict prognosis
    - miRNA (encouraging)

Kanda et al. Mutant GNAS detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. Gut 2013; 62:7 1024-1033

Multicenter, retrospective study of 130 resected patients with 12 SCA, 10 SPPN, 12 MCN and 96 IPMN

Cyst fluid analyzed to identify
  - BRAF, CDKN2A, CTNNB1, GNAS, KRAS, NRAS, PIK3CA, RNF43, SMAD4, TP53 and VHL

Analyses performed with specialized technologies for implementing and interpreting massively parallel sequencing data acquisition

Springer et al. A Combination of Molecular Markers and Clinical Features Improve the Classification of Pancreatic Cysts. Gastroenterology 2015 In press.
Pancreatic Cysts: Medical & Endoscopic Management

An algorithm was used to select markers that could classify cyst type and grade

Authors identified molecular markers and clinical features that classified cyst type with
- 90%-100% sensitivity
- 92%-98% specificity

Molecular marker panel correctly identified
- 67/74 patients who did not require surgery

Results of this study could reduce the number of unnecessary operations by 91%

---

EUS-Guided Ethanol Ablation Studies

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Patients</th>
<th>Symptoms</th>
<th>Cyst size mm</th>
<th>Agent used</th>
<th>F/up (mo)</th>
<th>Resolution %</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gan 2005</td>
<td>25</td>
<td>no</td>
<td>19 (6-37)</td>
<td>Etanol</td>
<td>6-12</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td>Oh 2008</td>
<td>14</td>
<td>no</td>
<td>25.5 (17-52)</td>
<td>Etanol + Paclitaxel</td>
<td>31</td>
<td>79</td>
<td>Pain = 1, AP = 1</td>
</tr>
<tr>
<td>Oh 2009</td>
<td>10</td>
<td>no</td>
<td>29.5 (20-68)</td>
<td>Etanol + Paclitaxel</td>
<td>8.5</td>
<td>60</td>
<td>AP = 1</td>
</tr>
<tr>
<td>DeWitt 2009</td>
<td>42</td>
<td>no</td>
<td>10-50</td>
<td>Etanol vs saline</td>
<td>3-4</td>
<td>33</td>
<td>Pain = 10, AP = 2</td>
</tr>
<tr>
<td>Oh 2011</td>
<td>47</td>
<td>no</td>
<td>31.8 (17-68)</td>
<td>Etanol + Paclitaxel</td>
<td>21.7</td>
<td>62</td>
<td>AP = 1, SV occl. = 1</td>
</tr>
<tr>
<td>DiMaio 2011</td>
<td>13</td>
<td>no</td>
<td>20</td>
<td>Etanol</td>
<td>13</td>
<td>38</td>
<td>-</td>
</tr>
<tr>
<td>DeWitt 2014</td>
<td>22</td>
<td>pain=55%, none=45%</td>
<td>25 (15-43)</td>
<td>Etanol + Paclitaxel</td>
<td>27</td>
<td>50</td>
<td>AP = 3, Peritonitis = 1</td>
</tr>
<tr>
<td>Gomez In press</td>
<td>23</td>
<td>Not stated</td>
<td>&gt;10</td>
<td>Etanol</td>
<td>40</td>
<td>52</td>
<td>AP=1, PC=1</td>
</tr>
</tbody>
</table>
Back to the case presentation

Surgery

• Whipple’s procedure
  • IPMN (LGD) extensively involving the majority of the resected specimen
  • Largest gross lesion 1.2 cm
  • Negative margins
• Follow up (9 yrs)
  • Normal pancreas remnant (CT)

Take Home Messages

• Asymptomatic, small pancreatic cysts increasingly diagnosed (elderly)
• Guidelines suggest observation (limited)
• Combined clinical and imaging correct dx 70%
• Promising data from panel of molecular markers to select patients who can avoid surgery
• EUS-guided ethanol (+ paclitaxel)
  • Current results do not support its use in routine practice
Auto-Immune Pancreatitis

Suresh T. Chari, MD, FACG
Division of Gastroenterology and Hepatology
Mayo Clinic
Rochester

Steroid-Responsive Chronic Pancreatitis

Two distinct steroid-responsive chronic fibro-inflammatory diseases of the exocrine pancreas
- Type 1 AIP
- Type 2 AIP

Both diseases characterized by:
- Pathognomonic pancreatic histo-pathology
- Frequent presentation with obstructive jaundice
- Dramatic response to steroid treatment

These commonalities lead to use of term “AIP” for both
Pancreas 2010;39:549-54
Gastroenterology 2015;149(1):39-51
Steroid-Responsive Chronic Pancreatitides

Though both conditions are called AIP, they are really 2 distinct diseases

To avoid confusion it has recently been suggested that
• the term AIP be reserved for type 1 AIP
• “idiopathic duct-centric chronic pancreatitis (IDCP)” be used for type 2 AIP

Gastroenterology 2015;149:39-51

Comparison of Clinical Profiles of AIP and IDCP

<table>
<thead>
<tr>
<th></th>
<th>AIP (N=78)</th>
<th>IDCP (N=43)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years) (mean)</strong></td>
<td>61.8</td>
<td>30.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Gender Male (%)</strong></td>
<td>77%</td>
<td>53.5%</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Acute pancreatitis/Other- mostly OJ)</td>
<td>12 (15%)</td>
<td>25 (58%)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Imaging</strong></td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Diffuse swelling</td>
<td>31 (40%)</td>
<td>3 (16%)</td>
<td></td>
</tr>
<tr>
<td>Other features</td>
<td>47 (60%)</td>
<td>16 (84%)</td>
<td></td>
</tr>
<tr>
<td><strong>Serum IgG4 elevation (&gt;140 mg/dl)</strong></td>
<td>47/59 (80%)</td>
<td>2/43 (6%)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Other organ involvement</strong></td>
<td>47 (60%)</td>
<td>0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Inflammatory Bowel Disease</strong></td>
<td>6%</td>
<td>37.5%</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Gastroenterology 2010 Jul;139:140-8; Gut doi:10.1136/gutjnl-2015-309275
Uncommon (rare) disorders
IDCP rarer than AIP
Both mimic more common disorders
Intense interest in diagnosing them as they are both treatable

AIP: Part of a Multi-organ Disorder
Initially described as associated with other autoimmune disorders, such as Sjogren’s syndrome and primary sclerosing cholangitis
Now clear that AIP is the pancreatic manifestation of the multi-organ IgG4-related disease (IgG4-RD) which may involve virtually any organ in the body
Previously noted “associations” are part of multi-organ involvement in IgG4-RD
Most involved organs show similar characteristics
• Lancet 2015;385,Issue 9976:460–1471
IgG4-Related Disease: Not a Pancreas-specific Disorder

Adapted from: Chari & Murray Gastroenterology 2008;164:265-7

AIP: Clinical Profile

Majority (~70%)
- Males
- Age >50 years
  Very rare in children and young adults (do not look for it in this age group!)
- Presentation with obstructive jaundice
- Serum IgG4 elevation
- Other organ involvement

All patients
- Have diagnostic histology (if available)
- Respond to steroids
Cardinal Features: The HISORt Criteria

- Histology and immunostaining
- Imaging
- Serology
- Other organ involvement
- Response to steroid therapy

Best developed for autoimmune pancreatitis and to a lesser extent for IgG4 associated cholangitis

- Chari et al Clin Gastroenterol Hepatol 2006;4:1010-6

Histology

Diagnosis only possible on core biopsy or resection as it needs architecture

Cytology not adequate to make a diagnosis

- More to exclude cancer
Core Biopsy of Pancreas in AIP

Diffuse Lymphoplasmacytic Infiltrate centered around pancreatic ducts and ductules
Lymphoplasmacytic sclerosing pancreatitis

i. Dense periductal lymphoplasmacytic infiltrates, without duct destruction

ii. Diffuse fibrosis, often storiform

iii. Obliterative phlebitis

iv. Many IgG4-positive cells (>10/hpf)

Definite: 3 / 4, Compatible: 2 / 4

Characteristic Pancreatic Imaging
(seen in 40%)
Serologic Abnormalities in AIP

Commonly elevated (>50%) of patients
- IgG (60%)
- IgG4 (75%)
- IgE (60%)

Less common (25-50%)
- Eosinophilia
- Low complement
- Titers of ANA, rheumatoid factor and auto-antibodies to lactoferrin, carbonic anhydrase

Uncommon (<25%):
- Elevated CRP

Mayo Clin Proc. 2015;90(7):927-939

Serum IgG4 in AIP/IgG4-RD

Sensitivity: 60-80%
Not specific!
Positive predictive value 10%!!
Measure it only if the clinical picture fits
Other Organ Involvement: Important Clue

Response to Steroid Therapy
Steroid-responsive Pancreatic Mass

Resolution of Distal Biliary Stricture
Resolution of Proximal Biliary Stricture

8 weeks later

Diagnosis of AIP/IgG4-RD

Diagnostic histology in an affected organ

Or

A diagnostic combination of features including histology, imaging, serology (serum IgG4), other organ involvement and response to steroids
Treatment of AIP/IgG4-RD: General Principles

- Make the diagnosis
- Induce remission
- Maintain remission

Symptomatic, Radiologic, Serologic and Histologic Remission

- Sustained clinical remission
- Early and late relapse
- Withdrawal of maintenance therapy

Re-institution of induction followed by maintenance therapy

Therapy

- Steroids:
  - Induce remission
  - Can maintain remission, though relapses occur on low-dose steroids
Therapy

• Immuno-modulators
  • Azathioprine, mycophenolate mofetil, methotrexate
  • Cannot induce remission, maintain it in 50%

Therapy

• B-cell depletion therapy
  • Rituximab
    • Single agent
    • Induces and maintains remission

• Appropriate as first agent if
  • Previous serious steroid intolerance
  • Multi-organ involvement
Natural History

Spontaneous or drug-induced remission
• Not durable
• 50% relapse, either in pancreas or other organs
• Relapses are treatment-responsive

Relapsers need maintenance therapy
Its propensity to promote cancer not proven

AIP: Summary

Part of IgG4-RD, an emerging multisystem disease entity
Mimics many well known diseases, especially as tumors
Diagnosis can be challenging
Correct diagnosis can prevent major surgery
Highly steroid responsive
Idiopathic Duct-centric Chronic Pancreatitis

Described initially as a distinct histopathological pattern seen in idiopathic chronic pancreatitis
  • Non-alcoholic duct-destructive CP
    Gut 1997;41:263-268

Subsequently shown to be associated with a distinct clinical profile
  • Idiopathic duct-centric CP
    Gastroenterology 2010 Jul;139:140-8;
    Gut doi:10.1136/gutjnl-2015-309275
IDCP

Characterized by:
- Lobular neutrophilic infiltrate
  - When severe microabscesses
- Intraepithelial inflammation
  - When severe duct destruction/obliteration
- None to minimal IgG4+ cells

Pancreas 2010;39:549-54

IBD and IDCP

Gut doi:10.1136/gutjnl-2015-309275
IDCP

Treatment

Spontaneous or steroid-induced remission

Inflammation exquisitely steroid-sensitive

Usually only one 3-month course of steroids

Natural History

Recurrences rare (<10%)

May destroy the gland during healing leading to exocrine and endocrine failure
Summary

Two steroid responsive pancreatitides
  • AIP
  • IDCP

Distinct diseases
  • Clinical profile
  • Serology
  • Natural history
  • Pathogenesis
Controversies in the Treatment of Acute Pancreatitis

Timothy B. Gardner, MD, MS, FACG
Associate Professor of Medicine
Geisel School of Medicine at Dartmouth
Director, Pancreatic Disorders
Medical Director, Islet Cell Transplant Program
Section of Gastroenterology and Hepatology
Dartmouth-Hitchcock Medical Center

Objectives

1. Fluid Resuscitation
Objectives

1. Fluid Resuscitation

2. Antibiotic Therapy

3. Nutritional Support
Objectives

1. Fluid Resuscitation
2. Antibiotic Therapy
3. Nutritional Support
4. Fluid Collections

Acute Pancreatitis

Table 3. Gastrointestinal and Hepatology Principal Discharge Diagnoses from Hospital Admissions, 2009

ACG Treatment Guideline

Case Presentation - Pancreatitis

Chief Complaint:  Epigastric abdominal pain

History of Present Illness:
- 52 y/o male
- Chronic alcoholism
- 24 hours of epigastric pain with radiation to back
- Febrile to 39.5°

- WBC count  = 21,235  
- Lipase  = 1,243
- BUN/CR  = 52/1.6

HCT = 49
TB = 1.2  AP = 96
AST/ALT = 41/32
Case Presentation - Pancreatitis

Questions to Consider

- What fluid orders do I write?
- Should I put him on antibiotics?
- How should I feed him?
Objectives

1. Fluid Resuscitation

2. Antibiotic Therapy

3. Nutritional Support

4. Fluid Collections

Fluid Resuscitation

Alterations in the Pancreatic Microcirculation

- Hypovolemia
- Increased Permeability – free radicals
- Microthrombi

Acinar Cell Injury
- Proinflammatory mediators
  (TNF, Bradykinin, IL-1, IL-6)

Further Capillary Vasconstriction
- Release of second stage proinflammatory mediators

ACG 2015 Annual Postgraduate Course
Copyright 2015 American College of Gastroenterology
Fluid Resuscitation

Recommendations based on Expert Opinion Only

Table 1. Fluid Resuscitation Recommendations From Recent Reviews of Acute Pancreatitis

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Journal</th>
<th>Initial resuscitation recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pandol et al.</td>
<td>Gastroenterology, 2007</td>
<td>Severe volume depletion: 500-1000 cc/h</td>
</tr>
<tr>
<td>Forsmark and Baillie</td>
<td>Gastroenterology, 2007</td>
<td>Nonconcentrated fluid loss: 200-500 cc/h</td>
</tr>
<tr>
<td>Banks and Proctor</td>
<td>Am J Gastroenterol, 2006</td>
<td>Vigorous fluid resuscitation</td>
</tr>
<tr>
<td>Vego et al.</td>
<td>JAMA, 2004</td>
<td>Urine output ≤0.5 mL/kg body weight/h</td>
</tr>
<tr>
<td>Tenner</td>
<td>Am J Gastroenterol, 2004</td>
<td>Fluid bolus to achieve hemodynamic stability followed by 250-500 mL/h of crystalloids</td>
</tr>
</tbody>
</table>

Aggressive fluid resuscitation
At least 250-300 cc/h for 48 hours

Gardner et al. CGH 2008;6:1070-6

Fluid Resuscitation

Prospective Trials of Fluid Resuscitation in AP

---

Copyright 2015 American College of Gastroenterology
Fluid Resuscitation

Table 4. Effect of extreme hemodilution on prognosis

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Rapid hemodilution (HCT &lt;35%)</th>
<th>Slow hemodilution (HCT ≥55%)</th>
<th>P values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balthazar CT Scores</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission</td>
<td>6.1±1.7</td>
<td>5.7±2.1</td>
<td>0.26</td>
</tr>
<tr>
<td>1 week</td>
<td>7.1±2.2</td>
<td>6.8±1.4</td>
<td>0.39</td>
</tr>
<tr>
<td>2 weeks</td>
<td>7.3±2.5</td>
<td>7.2±2.2</td>
<td>0.997</td>
</tr>
<tr>
<td>Time interval for sepsis presented (d)</td>
<td>7.4±1.9</td>
<td>10.2±2.3</td>
<td>0.000</td>
</tr>
<tr>
<td>Incidence of sepsis (%)</td>
<td>78.6 (44/56)</td>
<td>57.6 (34/59)</td>
<td>0.016</td>
</tr>
<tr>
<td>In-hospital Survival rate (%)</td>
<td>66.1 (37/56)</td>
<td>84.7 (50/59)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis

Fluid Resuscitation

Prospective Trials of Fluid Resuscitation in AP

- Praised for large number of patients and only those with SAP included
- Criticized for a somewhat unusual treatment approach
Fluid Resuscitation

Study Design

Goal-Directed Therapy

Standard of Care Therapy

Group 1

Group 2

Group 3

Group 4

**Fluid Resuscitation**


**Fluid Resuscitation**

Fluid Resuscitation

**Recommendations**

- 20 ml/kg bolus and then 3 ml/kg/hr infusion for first 24 hours
- Lactated Ringer’s should be used as the fluid of choice over normal saline
- Patients must be watched closely for signs of over-aggressive resuscitation

---

Objectives

1. Fluid Resuscitation
2. Antibiotic Therapy
3. Nutritional Support
4. Fluid Collections
**Antibiotic Therapy**

**Admission Antibiotics**
“Do they prevent a bad clinical outcome?”

**Infected Pancreatic Necrosis**
“Can we get away with medical therapy only?”

---

**IMIPENEM FOR INFECTED NECROSIS**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Treatment</th>
<th>Control</th>
<th>Odds Ratio</th>
<th>Weight</th>
<th>Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perdoni 1999</td>
<td>5/41</td>
<td>10/33</td>
<td>3.90</td>
<td>0.02</td>
<td>[0.40, 0.105]</td>
</tr>
<tr>
<td>Nordback 2001</td>
<td>1/25</td>
<td>0/33</td>
<td>1.76</td>
<td>0.09</td>
<td>(0.02, 1.67)</td>
</tr>
<tr>
<td>Nosse 2007</td>
<td>2/13</td>
<td>4/14</td>
<td>2.55</td>
<td>0.01</td>
<td>[0.09, 3.99]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>78</strong></td>
<td><strong>82</strong></td>
<td><strong>1.00</strong></td>
<td><strong>1.00</strong></td>
<td><strong>0.34</strong> [0.13, 0.84]</td>
</tr>
</tbody>
</table>

**Imipenem Does Prevent Infected Necrosis**

Villatoro et al. Cochrane Database Sys Rev 2010
Antibiotic Therapy

Admission Antibiotics
“Do they prevent a bad clinical outcome?”

ALL ANTIBIOTICS - MORTALITY

Vilatoro et al. Cochrane Database Sys Rev 2010

Antibiotics Do Not Improve Mortality

Antibiotic Therapy

Infected Pancreatic Necrosis
“Can we get away with medical therapy only?”

Garg et al. Clin Gastro and Hepatology 2010;8:1089-4
Antibiotic Therapy

Infected Pancreatic Necrosis
“Can we get away with medical therapy only?”

Mouli et al. Gastroenterology 2013;144:333-40

<table>
<thead>
<tr>
<th>Table 1. Study Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>Group A</td>
</tr>
<tr>
<td>Frizzi et al^{a}</td>
</tr>
<tr>
<td>Söling et al^{a}</td>
</tr>
<tr>
<td>Lee et al^{b}</td>
</tr>
<tr>
<td>Looij et al^{c}</td>
</tr>
<tr>
<td>Leem et al^{d}</td>
</tr>
<tr>
<td>Gock et al^{b}</td>
</tr>
</tbody>
</table>

Group B:

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Country</th>
<th>Study design</th>
<th>Study period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raski et al^{a}</td>
<td>1996</td>
<td>United States</td>
<td>Retrospective observational study</td>
<td>1991-1995</td>
</tr>
<tr>
<td>Noth et al^{a}</td>
<td>2006</td>
<td>Portugal</td>
<td>Retrospective observational study</td>
<td>1993-2003</td>
</tr>
<tr>
<td>Revankar et al^{d}</td>
<td>2008</td>
<td>Germany</td>
<td>Retrospective observational study</td>
<td>1993-2004</td>
</tr>
<tr>
<td>Mottet et al^{c}</td>
<td>2009</td>
<td>United States</td>
<td>Retrospective observational study</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

Mouli et al. Gastroenterology 2013;144:333-40
**Antibiotic Therapy**

**Infected Pancreatic Necrosis**

“Can we get away with medical therapy only?”

64% successfully treated with medical therapy

Mouli et al. Gastroenterology 2013;144:333-40

<table>
<thead>
<tr>
<th>Study</th>
<th>Success of primary conservative management (95% CI)</th>
<th>Success (95% CI)</th>
<th>Weight (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rundl et al.</td>
<td>0.50 (0.31, 0.69)</td>
<td>11.89</td>
<td></td>
</tr>
<tr>
<td>Song et al.</td>
<td>0.70 (0.61, 0.87)</td>
<td>11.85</td>
<td></td>
</tr>
<tr>
<td>Lee et al.</td>
<td>0.71 (0.55, 0.87)</td>
<td>12.49</td>
<td></td>
</tr>
<tr>
<td>Gang et al.</td>
<td>0.85 (0.43, 0.66)</td>
<td>13.70</td>
<td></td>
</tr>
<tr>
<td>van Santvoort et al.</td>
<td>0.35 (0.21, 0.49)</td>
<td>12.56</td>
<td></td>
</tr>
<tr>
<td>Pan et al.</td>
<td>0.85 (0.77, 0.92)</td>
<td>14.40</td>
<td></td>
</tr>
<tr>
<td>Gluck et al.</td>
<td>0.76 (0.58, 0.94)</td>
<td>11.87</td>
<td></td>
</tr>
<tr>
<td>Amedia et al.</td>
<td>0.65 (0.44, 0.86)</td>
<td>11.14</td>
<td></td>
</tr>
<tr>
<td>Overall (I-squared = 90.3%, P = .002)</td>
<td>0.64 (0.51, 0.78)</td>
<td>100.00</td>
<td></td>
</tr>
</tbody>
</table>

**Antibiotic Therapy**

**Recommendations**

- Imipenem can be used to prevent infected necrosis, but does not influence mortality in predicted SAP
- Patients with infected pancreatic necrosis can be managed non-operatively
- Randomized trials are needed to further define these recommendations
Objectives

1. Fluid Resuscitation
2. Antibiotic Therapy
3. Nutritional Support
4. Fluid Collections

Nutritional Support

Enteral vs Parenteral Nutrition for Acute Pancreatitis: Mortality

Enteral Nutrition Improves Mortality

Nutritional Support

Enteral vs. Parenteral Nutrition for Acute Pancreatitis

Randomized to nasoenteric or oral feeding within 72 hours

Bakker et al. NEJM 2014;371:183-93.

Nutritional Support

Recommendations

- Use the gut as early as possible
- Even trophic feeds can be helpful to prevent bacterial translocation into necrotic tissue
- Per os feeding is a proven means of initiating feeding – no clear benefit to NJ vs NG feeding
Objectives

1. Fluid Resuscitation

2. Antibiotic Therapy

3. Nutritional Support

4. Fluid Collections

Fluid Collections

- Pancreatic fluid collections arise as complications of acute pancreatitis

- There are multiple types of pancreatic fluid collections, but all arise in the context of *pancreatic ductal disruption or injury*
**Fluid Collections**

It is **CRITICAL** to understand this classification system because treatment varies depending on the type of collection.

### Table 1. Revised Atlanta Classification for fluid collections in acute pancreatitis

<table>
<thead>
<tr>
<th>Entity</th>
<th>Type of pancreatitis</th>
<th>Time course, wk</th>
<th>Solid debris present</th>
<th>Encapsulated wall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute fluid collection</td>
<td>Interstitial</td>
<td>&lt;4</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Acute necrotic collection</td>
<td>Necrotic</td>
<td>&lt;4</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pseudocyst</td>
<td>Interstitial</td>
<td>&gt;4</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Walled-off necrosis</td>
<td>Necrotic</td>
<td>&gt;4</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*The classification provides general guidelines; some collections may be difficult to categorize.*

Gardner. Endoscopic Management of Necrotizing Pancreatitis. GIE 2012
Fluid Collections

Delay

Acute Fluid/Necrotic Collection

DRAIN

Pseudocyst

DEBRIEDE

Walled-off Necrosis
**Fluid Collections**

*Standard Cystgastrostomy/Duodenostomy Drainage*

1. Cavity puncture (cystgastrostomy or cystduodenostomy)
2. Dilation of fistula tract
3. Placement of drainage stents
4. Cavity irrigation
5. Replacement/removal of stents

---

**Fluid Collections**

*Pseudocyst*
Fluid Collections

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Surgery (n = 10)</th>
<th>EUS (n = 20)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technical success (%)</td>
<td>100</td>
<td>100</td>
<td>1.000</td>
</tr>
<tr>
<td>Treatment success (%)</td>
<td>100</td>
<td>95</td>
<td>.964</td>
</tr>
<tr>
<td>Reinfection (%)</td>
<td>10</td>
<td>0</td>
<td>.512</td>
</tr>
<tr>
<td>Complication (%)</td>
<td>0</td>
<td>0</td>
<td>.000</td>
</tr>
<tr>
<td>Length of stay (d)</td>
<td>Mean (range) 6.5 (range 4-20)</td>
<td>2.6 (range 1-11)</td>
<td>.008</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean cost (US$)</td>
<td>14,815</td>
<td>9,077</td>
</tr>
</tbody>
</table>

Fluid Collections

- Acute Fluid/Necrotic Collection
- Pseudocyst
- Walled-off Necrosis

DELAY

DRAIN

DEBRIDE

**TABLE 2. Outcome of surgical versus EUS-guided cyst-gastrostomy**

**TABLE 3. Mean hospital costs for surgery and EUS groups**

Varadarajulu et al. GIE 2008;68(4):649-55
Open surgical debridement should almost never be performed.
Fluid Collections

Bakker et al. JAMA 2012;307:1053-61

Fluid Collections

How successful is this procedure?

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Successful resolution, no. (%)*</th>
<th>95 (91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months to cavity resolution after intervention (95% CI)</td>
<td>4.1 (3.3-4.6)</td>
<td></td>
</tr>
<tr>
<td>Total in-hospital days after initial drainage, mean (95% CI)</td>
<td>12 (9-15)</td>
<td></td>
</tr>
<tr>
<td>Recurrent collection, no. (%)</td>
<td>6 (6)</td>
<td></td>
</tr>
<tr>
<td>Recurrent pancreatitis, no. (%)</td>
<td>3 (3)</td>
<td></td>
</tr>
</tbody>
</table>

*Success defined as resolution or near-resolution (>90%) of cavity without operative or percutaneous drainage of the cavity.
†Recurrence of collection more than 6 months after initial resolution.
‡Of the patients who had recurrence had unsuccessful cavity resolution.

Fluid Collections

Are there any comparative effectiveness trials?

A Step-up Approach or Open Necrosectomy for Necrotizing Pancreatitis

VARDS vs. OPEN NECROSECTOMY

Van Santvoort et al. NEJM 2010; 362(16):1491-1502

Fluid Collections

PANTER TRIAL - CONCLUSIONS

Van Santvoort et al. NEJM 2010; 362(16):1491-1502
Are there any comparative effectiveness trials specific to endoscopy?

**Endoscopic Transgastric vs Surgical Necrosectomy for Infected Necrotizing Pancreatitis**

A Randomized Trial

**DIRECT ENDOSCOPIC NECROSECTOMY vs. VARDS**

Bakker et al. *JAMA* 2012; 307(10):1053-61

**Fluid Collections**

**PENGUIN TRIAL - METHODOLOGY**

<table>
<thead>
<tr>
<th>Event</th>
<th>Surgical Necrosectomy (n = 10)</th>
<th>Endoscopic Transgastric Necrosectomy (n = 10)</th>
<th>Risk Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major complications or death, No. (%)²</td>
<td>8 (80)</td>
<td>2 (20)</td>
<td>0.60 (0.10 to 0.80)</td>
<td>.01</td>
</tr>
<tr>
<td>Death, No. (%)</td>
<td>4 (40)</td>
<td>1 (10)</td>
<td>0.50 (-0.06 to 0.60)</td>
<td>.30</td>
</tr>
<tr>
<td>New complications, No. (%)²</td>
<td>5 (50)</td>
<td>1 (10)</td>
<td>0.50 (0.12 to 0.78)</td>
<td>.03</td>
</tr>
<tr>
<td>New-onset diabetes</td>
<td>3 (30)</td>
<td>2 (20)</td>
<td>0.81 (0.07 to 0.81)</td>
<td>.04</td>
</tr>
<tr>
<td>Persistent fluid collections²</td>
<td>3 (30)</td>
<td>2 (20)</td>
<td>0.94 (0.07 to 0.94)</td>
<td>.33</td>
</tr>
<tr>
<td>Pancreatic fistula</td>
<td>7 (70)</td>
<td>1 (10)</td>
<td>0.60 (0.17 to 0.81)</td>
<td>.02</td>
</tr>
<tr>
<td>Long-term complications, No. (%)²</td>
<td>10 (9)</td>
<td>8 (8)</td>
<td>.60 (-0.17 to 0.30)</td>
<td>.33</td>
</tr>
<tr>
<td>No. of necrosectomies, endoscopic or surgical</td>
<td>1 (1) to 2</td>
<td>6 (6) to 10</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td>Days in hospital after randomization, No. (%)</td>
<td>36 (17 to 74)</td>
<td>45 (12 to 68)</td>
<td>.91</td>
<td></td>
</tr>
</tbody>
</table>

Bakker et al. *JAMA* 2012; 307(10):1053-61
**Fluid Collections**

**STENTS**

What Type?  How Many?  Do they need to be removed?

---

**Recommendations**

- It is imperative to accurately classify fluid collections because this determines appropriate intervention.

- Minimally invasive techniques, including endoscopic drainage/debridement appear to be safer and equally efficacious as surgical approaches.

- Randomized trials are needed to further define these recommendations.
Controversies (cont)

- What is the role of anticoagulation for venous thrombosis?
- Do antiproteases have a role in severe AP – aka continuous regional arterial infusion?
- Are we at the point where targeted anti-inflammatory therapies can be tried in AP?
Emerging Approaches to PBC and PSC

Keith D. Lindor, MD, FACG
Dean, College of Health Solutions
Arizona State University

OUTLINE

PBC
- Epidemiology
- Diagnosis
- Treatment

PSC
- Natural History
- Treatment
- Cancer
Predictors of Prognosis


Higher APRI is Associated with Poorer Transplant-Free/Overall Survival in PBC

Survival Rates, Elastography & PBC

Role of Liver Biopsy in PBC

If:
- ⊕AMA
- Alk Phos >1.5 times nl
- AST <5 times normal

Then:
- Positive predictive value for PBC >98%
  - (sensitivity 80%, specificity 92%)

Predictors of Esophageal Varices in PBC

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet Count</td>
<td>&lt;140,000</td>
</tr>
<tr>
<td>Mayo Risk Score</td>
<td>≥4.5</td>
</tr>
</tbody>
</table>
### Medical Approaches to PBC UDCA

Survival Free of Transplantation
Combined Data

<table>
<thead>
<tr>
<th>Group</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>UDCA</td>
<td>273</td>
</tr>
<tr>
<td>Placebo &amp; UDCA</td>
<td>275</td>
</tr>
<tr>
<td>Survival Rate %</td>
<td>236</td>
</tr>
<tr>
<td></td>
<td>220</td>
</tr>
<tr>
<td></td>
<td>87</td>
</tr>
</tbody>
</table>


Survival in PBC

Treated vs. Untreated
Treated vs. Population

Natural History of PBC Effects of UDCA

Ursodiol Alone

- Biochemical normalization in ~1/3
- Risk scores or alkaline phosphatase response predictive
- Various drugs tried in combination

Combination Therapy for PBC
Biochemical Endpoints for Predicting Outcomes

Newer Therapies for PBC

- Bezafibrate/Fenofibrate
- Silymarin
- B cell antibodies
- FXR agonists
OCA Treatment in Patients with PBC


Pruritus Severity in PBC Patients with OCA

Conclusion Regarding Drug Therapy

When UDCA is not adequate:
- Doubling dose is not helpful
- No clear, proven choices
- Many promising adjuncts being investigated

Hepatocellular Cancer Risk in PBC

- 18 Patients over 25 years
- Multivariate Analysis

<table>
<thead>
<tr>
<th></th>
<th>O.R</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.6</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Male</td>
<td>5.6</td>
<td>&lt;.05</td>
</tr>
<tr>
<td>Hx Transfusion</td>
<td>4.7</td>
<td>&lt;.07</td>
</tr>
<tr>
<td>Mayo Risk</td>
<td>1.3</td>
<td>&lt;.02</td>
</tr>
</tbody>
</table>
Hepatocellular Carcinoma in PBC

Survival probability

Conclusions About PBC

- Becoming more common
- Slowly progressive, even if asymptomatic
- Prognostic markers helpful
- UDCA improves natural history
- Cancer risk is present
Histologic Features of PSC
Liver Transplantation for PBC & PSC

PSC Survival in Olmsted County Minnesota
Ursodiol in PSC

High-dose Urso for PSC Results

<table>
<thead>
<tr>
<th>Primary Endpoints</th>
<th>UDCA</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Liver Transplant</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Minimal Listing Criteria for Liver Transplant</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Development of Cirrhosis</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Esophageal and/or Gastric Varices</td>
<td>15</td>
<td>5</td>
</tr>
<tr>
<td>Cholangiocarcinoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total Endpoints</strong></td>
<td><strong>52</strong></td>
<td><strong>29</strong></td>
</tr>
</tbody>
</table>
Results

Model Of All Primary Endpoints
Adjusted For Mayo Risk Score, Presence of Varices, and Stage

Kaplan-Meier Analysis of Endpoint Free Survival in all PSC Patients with UDCA Treatment
Immunosuppressive and Other Agents

- Azathioprine
- Budesonide
- Docosahexaenoic acid
- Methotrexate
- Metronidazole
- Minocycline
- Mycophenolate mofetil
- Nicotine
- Pentoxifylline
- Pirfenodone
- Prednisolone
- Tacrolimus
- Vancomycin

Vancomycin & Metronidazole in PSC
Autoimmune Pancreatitis/Cholangitis in PSC

- IgG4 elevated in 9% PSC patients
- These patients have more aggressive disease
- These patients may be more steroid responsive.

Natural History “PSC” & IgG4

Association of IgG4 and Colectomy


Incidence of Cholangiocarcinoma
Elevated CA 19-9 Values in PSC

*7 bars represent interquartile range of the values

Colon Cancer/IBD/PSC

Risk %

- PSC/CUC
- CUC

9% 2% 5% 10%
10 Years 20 Years 25 Years
High-Dose Urso in UC & PSC Patients

Eaton J, Silveira MG, Pardi DS, et al. High-dose ursodeoxycholic acid is associated with the development of colorectal neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. Am J Gastroenterol 2011;106(9):1638-45

UDCA and Risk of Colorectal Neoplasia in Patients with PSC - IBD

UDCA and Risk of Advanced Colorectal Neoplasia in Patients with PSC - IBD


PBC
- Ursodiol is treatment
- Obeticholic acid promising
- Liver cancer risk present

PSC
- No established therapy
- Ursodiol role being defined
- High does UDCA (28 – 30 mg/kg/day) to be avoided
- Risk of bile duct and colon cancer