A paradigm shift in the management of pancreatic fluid collections—one puddle at a time

Abdul Haseeb MD MPH
Disclosures

• I have no financial relationships to disclose
• I will discuss off label use of devices
Objectives

• Pathophysiology of acute pancreatitis
• Fluid resuscitation protocols
• Identify complications related to pancreatitis
• Differentiate various pancreatic/extra pancreatic fluid collections
• Management of pancreatic necrosis
• Recognize potential complications
• Enteral nutrition
Acute Pancreatitis

- One of the most frequent gastrointestinal causes for hospital admission in the US.
- In 2015, AP accounted for approximately 390,000 hospitalizations.
  - 12% increase since 2006
  - 76% admitted from ED
  - 0.5% mortality
- Estimated inpatient costs of $2.6 billion annually
- Most cases are self-limited
- 15-20% can be severe
- 5-10% cases develop necrosis
  - 20%–30% mortality with infected necrosis

Barron T, Gastroenterology 2020
Perry AF, Gastroenterology 2015
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 = 21,000
- Lipase = 1300
- BUN/CR = 60/1.6

HCT = 49
TB = 1.4  AP = 96
AST/ALT = 52/32
Case Presentation - Pancreatitis

What fluid orders do I write?
Pathophysiology

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
Why early fluid resuscitation in AP

Animal studies:
• Microcirculation is impaired in experimental severe AP.
• Pancreatic vascular perfusion was attenuated by crystalloid infusion
  Knoefel et al, Surgery 1994
• Maintenance of volume status in hospitalized patients
• Acute inflammatory illness: therapeutic intervention
  • Improve local tissue perfusion
  • Oxygen delivery
• Impact disease course
  • Tissue necrosis
  • Organ failure
Fluid Resuscitation

Original article

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

MAO En-qiang, FEI Jian, PENG Yi-bing, HUANG Jie, TANG Yao-qing and ZHANG Sheng-dao

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 ≥35%)</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
Lactated Ringer’s Solution Reduces Systemic Inflammation Compared With Saline in Patients With Acute Pancreatitis

BECHIEN U. WU, JAMES Q. HWANG, TIMOTHY H. GARDNER, KATHRYN REPAS, RYAN DELEE, SONG YU, BENJAMIN SMITH, PETER A. BANKS, and DARWIN L. CONWELL
LR vs NS

Suggests LR better than NS

## RCTs on Rate of IVF

<table>
<thead>
<tr>
<th>Author</th>
<th>Design</th>
<th>N</th>
<th>Protocol</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| Mao     | RCT    | 115| Rapid hemodilution: goal hematocrit <35%  
Standard: goal hematocrit ≥0.35% in 48 hrs | Sepsis: 78.6 vs. 57.6%  
Death: 33.9 vs. 15.3% |
| Wu      | RCT    | 40 | Goal-directed: 20 mL/kg bolus + 3 or 1.5 mL/kg/hr  
Physician-directed | 24-hr SIRS reduction:  
84 vs. 0% |
| Buxbaum | RCT    | 60 | Aggressive: 20 mL/kg bolus + 3 mL/kg/hr  
Non-aggressive: 10 mL/kg bolus + 1.5 ml/kg/hr | Clinical improvement:  
70 vs. 42% |
Lactate suppresses inflammation

<table>
<thead>
<tr>
<th>Lactated Ringers</th>
<th>Normal Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH 6.5</td>
<td>pH 5.5</td>
</tr>
<tr>
<td>130 mEq Na</td>
<td>154 mEq Na</td>
</tr>
<tr>
<td>109 mEq Cl</td>
<td>154 mEq Cl</td>
</tr>
<tr>
<td><strong>28 mEq lactate</strong></td>
<td></td>
</tr>
<tr>
<td>4 mEq K</td>
<td></td>
</tr>
<tr>
<td>3 mEq Ca</td>
<td></td>
</tr>
</tbody>
</table>

## RCTs on type of IVFs

<table>
<thead>
<tr>
<th>Author</th>
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<th>N</th>
<th>Protocols</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wu, 2011</td>
<td>Three centers in USA</td>
<td>40</td>
<td>LR vs. NS</td>
<td>LR reduced SIRS (84% reduction vs. 0%, $p=0.035$) &amp; CRP at 24h (51.5 vs. 104 mg/dL, $p=0.02$) compared to NS</td>
</tr>
<tr>
<td>Choosakul, 2018</td>
<td>Single Center in Thailand</td>
<td>47</td>
<td>Goal-directed therapy with LR vs. NS</td>
<td>LR reduced 24-h SIRS (26% vs. 4%, $p=0.02$), <strong>but not 48h SIRS compared to NS</strong></td>
</tr>
<tr>
<td>De-Madaria, 2018</td>
<td>Single Center in Spain</td>
<td>40</td>
<td>Goal-directed therapy with LR vs. NS</td>
<td>LR reduced 48-h CRP (28 vs. 166 mg/L $p=0.04$) and 72-h CRP levels (25 vs. 217 mg/L $p=0.04$), <strong>but no 48-h and 72-h SIRS ($p=0.06$)</strong></td>
</tr>
</tbody>
</table>
Prospective and large retrospective studies

• Administration of >4.1L of IVFs during the first 24h associated with increased risk of persistent organ failure and acute fluid collections


• Aggressive fluid resuscitation in the first 4h associated with less need for invasive interventions, but was no difference in other outcomes

IMPROVED OUTCOME

Brown 2002
Gardner 2009
Wu 2011
Warndorf 2011
Buxbaum 2018

DETRIMENTAL

Eckerwall 2006
Mao 2010
de-Madaria 2011

Confusing?

Vege et al, Gastroenterology 2018
<table>
<thead>
<tr>
<th>AGA suggests using goal-directed therapy for fluid management.</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Conditional recommendation, very low quality evidence)</td>
</tr>
</tbody>
</table>

- Comment: The AGA makes no recommendation whether normal saline or Ringer’s lactate is used.

<table>
<thead>
<tr>
<th>Aggressive hydration, defined as 250 – 500 ml per hour.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most beneficial during the first 12 – 24hrs</td>
</tr>
<tr>
<td>(strong recommendation, moderate quality of evidence)</td>
</tr>
</tbody>
</table>

- Lactated Ringer preferred (conditional recommendation, moderate quality of evidence).
Phases of fluid resuscitation

Two phases of fluid resuscitation

**Early**: during **first 6hr** of presentation → with greater impact in outcomes

**Late**: 6-48hr: dependent on pt’s response to initial fluids. AP complications already set in (reverse causation bias)

What do we recommend

- 20 ml/kg bolus and then 3 ml/kg/hr infusion for first 24 hours with every 6 hr assessment (clinical/biochemical)

- Lactated Ringer’s is used as the fluid of choice over normal saline

- Watch closely for signs of over-aggressive resuscitation

Case Presentation - Pancreatitis

- Discharged home after 5 days of hospitalization on a low fat diet and a GI clinic f/u.
- He no-showed to the follow up appointment.
- Now, presents to ED 4 weeks later with abdominal pain, poor appetite and 6-8 lb weight loss.
- Denies any ongoing alcohol use.
  - Afebrile
  - Upper quadrant tenderness on exam
  - WBC count = 14,000
  - Hb=10
  - BUN/CR = 60/1.6
  - Lipase = 80
  - TB = 1.8  AP = 146  AST/ALT = 52/32
Complications

• Abdominal compartment syndrome
• Acidosis
• Acute renal failure
• Acute respiratory syndrome
• Ascites
• Bowel infarction
• Chronic pancreatitis
• Disseminated intravascular coagulation

• Gastric varices
• Ileus
• Mesenteric venous thrombosis
• Pancreatic Abscess
• Pancreatic arterial pseudoaneurysms
• Pancreatic necrosis
• Pseudocyst formation
• Splenic venous thrombosis
• Metabolic (hypocalcemia, hyperglycemia, hypertriglyceridemia)
• Neurological
Atlanta classification of collections
(1) acute peripancreatic fluid collections (APC)
(2) pseudocysts (PS)
(3) acute necrotic collections (ANC)
(4) walled off necrosis (WON)
Interstitial Pancreatitis

Necrotizing pancreatitis

Acute peripancreatic fluid collection

Acute Necrotic collection

Pancreatic pseudocyst

Walled off Necrosis

First 4 weeks

After 4 weeks

85%

15%

Banks PA, Gut 2013
Pancreatic and peri-pancreatic collections

Pancreatic pseudocyst
- Well defined wall
- Homogeneous fluid density
- No solid component
- Extra-pancreatic

Walled off Necrosis
- Well defined wall
- Heterogeneous with a mixed density
- Solid component
- Intra or extra pancreatic

Rare
Drainage alone
Simple to manage

Common
Drainage + Debridement
Multidisciplinary approach

Banks PA, Gut 2013
We avoid the term PFC as the majority are not pancreatic, but extra pancreatic or combined, and they are generally NOT FLUID!
Management Modalities

• Surgical
  - Open
  - Laparoscopic
  - Video-Assisted Retroperitoneal Debridement (VARD)

• Percutaneous
  - Catheter Drainage/Sinus tract Endoscopy

• Endoscopic (per oral)
  - Transluminal Drainage/Necrosectomy
  - Transpapillary drainage (rare)
Fig. 1. Possible routes taken during treatment of local complications of AP. 

- **a** Coronal view.
- **b** Sagittal view.

R1 = Per-os transpapillary; 
R2 = per-os transmural; 
R3 = percutaneous retroperitoneal; 
R4 = percutaneous transperitoneal; 
R5 = percutaneous transmural.
Evolution in Endoscopic Interventions

1. Plastic stents: Plastic tube with tails (off label)

2. Metal stents: Covered metal stent (off label)
   - Biliary

3. Lumen-apposing metal stents (LAMS): Purpose built covered metal stent to maintain lumen to lumen apposition while providing drainage port

Haseeb A, Clin Gastroenterol Hepatol. 2019
Timing of intervention

• When encapsulated: Treat the patient not the calendar
• Imaging review by an expert to assess whether encapsulation is present

- Infected collection
- Abd compartment syndrome

Needs immediate drainage.
Mostly percutaneous.

Early (<4 Weeks) Versus Standard (≥ 4 Weeks)
Endoscopically Centered Step-Up Interventions for Necrotizing Pancreatitis

Am J Gastro 2018
Guru Trikudanathan, MD1, Pierre Tawfik, MD2, Stuart K. Amateau, MD, PhD2, Satish Munigala MBBS, MPH1, Mustafa Arain, MD1, Rajeev Attam, MD1, Gregory Beilman, MD9, Siobhan Flanagan, MD1, Martin L. Freeman, MD1 and Shawn Mallery, MD1

Infection & Organ failure
Maximal supportive therapies

Case reviewed amongst interventional endoscopists

1. Compression of gastric outlet, bile duct, vessels
2. Infection
3. Persistent symptoms such as pain/unwellness/failure to thrive
4. ? Large size (>6 cm)

LUMC Approach to Pseudocyst drainage

The role of endoscopy in the diagnosis and treatment of inflammatory pancreatic fluid collections

Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE
V. Raman Mothusamy, MD, FASGE, Vinay Chandrasekhar, MD, Ruben D. Acosta, MD, David H. Bruning, MD, Krishnavel V. Charthadi, MD, Mohamad A. Elsoubeci, MD, MHS, FASGE, Ashley L. Fauns, MD, FASGE, Lisa Fonkalord, BSN, RN, CARN, SGNA representative, Suryakanth R. Gurudu, MD, FASGE, Moneen A. Khashab, MD, Shyamlal Kothari, MD, Jennifer R. Lighthead, MD, MPH, FASGE, NASPGHAN representative, Shabana F. Prash, MD, John R. Saltzman, MD, FASGE, Asmaa Shaukat, MD, MPH, FASGE, Amy Wang, MD, Julie Yang, MD, Brooks D. Cash, MD, FASGE, Previous Committee Chair, John M. DeWitt, MD, FASGE, Chair
Pseudocyst drainage

- Endoscopic transmural drainage – Preferred modality

- Endoscopic management vs surgery:
  - Substantially shorter hospital stay
  - Lower cost
  - Improved quality of life
  - Equivalent recurrence at 2-yrs
Pseudocyst drainage: Video
Interventions for Necrotizing Pancreatitis

Summary of a Multidisciplinary Consensus Conference

Martín L. Freeman, MD,* Jens Werner, MD,† Hjalmar C. van Santvoort, MD, PhD,‡
Todd H. Baron, MD,§ Marc G. Besselink, MD, PhD,|| John A. Windsor, MD,¶ Karen D. Horvath, MD,#
Eric vanSonnenberg, MD,** Thomas L. Bollen, MD,†† Santhi Swaroop Vege, MD,§
and An International Multidisciplinary Panel of Speakers and Moderators‡‡

AGA CLINICAL PRACTICE UPDATE: EXPERT REVIEW

American Gastroenterological Association Clinical Practice Update: Management of Pancreatic Necrosis

Todd H. Baron,¹ Christopher J. DiMaio,² Andrew Y. Wang,³ and Katherine A. Morgan⁴
Gold standard was open necrosectomy
- Complications: 34-95%
- Death: 6-26%
- Long term complications
  - Fistula
  - Diabetes
  - Pancreatic insufficiency
  - Hernias
Pancreatic Necrosis: PCD
Poorly demarcated infected necrosis + Sepsis
Radiologic approach to necrotizing pancreatitis: PCD

11 studies, 1 prospective
Total = 384 pts
Infected necrosis = 70.6%

No necrosectomy after
PCD=55%
Overall mortality = 17.4%

Limitations of PCD

- External pancreatic fistula > 25%
- Discomfort
- Inconvenience
- Poor outcomes with solid or poorly liquified necrosis

130 prospective patients with
PCD 1st
- PCD alone successful in 35%
- Mortality 20%
- Fistula formation 25%

TABLE 5. Bootstrap Validated Multivariable Regression Analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>0.27 (0.09–0.55)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>0.15 (0.04–0.62)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Percentage of necrosis</td>
<td>0.54 (0.30–0.96)</td>
<td>0.03</td>
</tr>
<tr>
<td>(&gt;30%/30%/50%/&gt;50%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30%–50%</td>
<td>0.48 (0.17–1.32)</td>
<td>0.15</td>
</tr>
<tr>
<td>&gt;50%</td>
<td>0.30 (0.90–1.02)</td>
<td>0.05</td>
</tr>
<tr>
<td>Heterogeneous collection</td>
<td>0.21 (0.06–0.67)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

* ≤24 hrs before drainage.
† On last CT before drainage.
VARD
Minimally invasive approach to infected necrosis superior to open surgery with respect to:
- short and long term mortality
- Organ failure
- Hernia
- Diabetes
Is endoscopic better than MIS?

• PENGUIN TRIAL (JAMA, 2012)
  Endoscopic Necrosectomy v VARD

• TENSION TRIAL (Lancet, 2018)
  Endoscopic Step Up versus Minimally Invasive Surgical Step UP (VARD)

• MISER TRIAL (Gastroenterology, 2019)
  Endoscopic Step Up versus Minimally Invasive Surgical (Lap vs VARD)
Dutch evolve management: endoscopic approach appears superior (PENGUIN)

Endoscopic Transgastric vs Surgical Necrosectomy for Infected Necrotizing Pancreatitis
A Randomized Trial

Table 2. Clinical End Points

<table>
<thead>
<tr>
<th>Major complications or death, No. (%)</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>Death, No. (%)</td>
<td>4 (40)</td>
<td>1 (10)</td>
<td>0.30 (-0.08 to 0.60)</td>
<td>.30</td>
</tr>
<tr>
<td>New-onset multiple organ failure</td>
<td>5 (50)</td>
<td>0 (0)</td>
<td>0.50 (0.12 to 0.76)</td>
<td>.03</td>
</tr>
<tr>
<td>Intra-abdominal bleeding requiring intervention</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterocutaneous fistula or perforation of a visceral organ requiring intervention</td>
<td>2 (20)</td>
<td>0 (0)</td>
<td>0.20 (-0.11 to 0.51)</td>
<td>.47</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>
</tbody>
</table>

Small randomized trial suggesting less mortality, organ failure or fistulae
OUTCOMES

- New-onset organ failure
- Enteral or pancreatic-cutaneous fistula
- Bleeding
- Perforation

MISER trial: primary endpoint was defined as a composite of major complications or death during a 6-month follow-up.

Endoscopic vs Surgical (11.8% vs 40.6%; risk ratio 0.29; P<007)
Endoscopic approach has less complications when compared to surgery.

Which stent to use for transluminal drainage?
• 60 patients randomized to LAMS (n=31) or plastic stent (n=29)
• No difference in stent-related adverse events (LAMS 6.5 vs. plastic 6.9%)
• No significant difference in treatment success, SIRS resolution, clinical adverse events, readmissions or hospital stay between cohorts
• Procedure duration was shorter for LAMS placement (15 vs. 40 min)
• Procedure cost (US$12,155 vs US$6,609) were higher
Maximal supportive therapies

Case reviewed amongst interventional endoscopists

Intervention indicated

1. Evidence of infection with deterioration
2. Ongoing organ failure several weeks after onset of AP
3. In sterile necrosis (once walled off)
   a) gastric outlet, intestinal, or biliary obstruction
   b) persistent symptoms (pain, ‘unwellness’)
   c) disconnected pancreatic duct

Near 15-20% do not require invasive intervention
Basic Principles - Drainage/Necrosectomy

• Never a one a done
  • 2-10 procedures are needed
  • Every 2-4 days
  • Take 2-3 hrs/procedure
• Lead to frequent and long-term hospitalizations
• Nutrition is the key
• Long term pain management

Jha A, JGH 2019
Necrosectomy procedure video

LAMS (15mm)
More than one approach

- Multiple Gateway Technique
- Combined Endoscopic + Percutaneous
- Sinus Tract Endoscopy
Systematic review, 14 observational studies
- 1100 endoscopic procedures/455 patients
- Mean 4 (range 1–23) sessions/pt
- Complications = 36%
- Procedure-related mortality = 6%

PPI after Necrosectomy

• PPI use leads to less acidic gastric content → impedes dissolution of solid necrosis.

• Study of 272 patients undergoing endoscopic drainage of WON
  • No difference in the technical success (100% vs. 98.8%, $P = 1$), or Clinical success rates (78.7% vs. 77.9%).
  • More necrosectomies needed in the PPI vs. non-PPI group (3.2 vs. 4.6 respectively, $P < 0.01$).
  • More stent occlusion in the PPI group vs. non- PPI group (20.1% vs 9.5% $P = 0.012$)

Without a pressing indication, we often STOP PPIs after transluminal drainage.
Maximal supportive therapies
Case reviewed among Interventional endoscopists

Maximally Encapsulated

Non-encapsulated

Adjacent to foregut without deep extension
Endoscopic intervention

Adjacent to foregut with deep extension
Endoscopic + Percutaneous ± STE/VARDS

Not adjacent to foregut
Percutaneous ± STE/VARDS

LUMC Modified Multidisciplinary Approach to Pancreatic necrosis
Nutritional support: Pancreatitis
Enteral vs Parenteral Nutrition and Early nutrition

Enteral Nutrition Improves Mortality


NO reduction in rate of infection or death

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

- Cochrane systematic review of 5 RCTS and 220 pts
  - showed that there was little or no difference between NG and NJ for death, success of feeding, and complications of feeding.  
    Dutta AK, Cochrane Database of Systematic Reviews 2020

- NG feedings may be problematic
  - Inadequate pancreatic rest
  - Poor tolerance with large collections, GOO, and ileus.

- A study of 36 healthy volunteers demonstrated that only TF administered beyond 20 cm from the ligament of Treitz successfully avoided pancreatic stimulation  
  Kaushik N, Pancreas 2005
Long-term jejunostomy access (percutaneous endoscopic gastrostomy with jejunal extension (PEG-J) or direct percutaneous endoscopic jejunostomy (DPEJ) or surgical jejunostomy) can be used in those requiring EN for more than 30 days. Grade of Recommendation GPP e Strong consensus (97% agreement).