Randomized Controlled Trials in Pancreatic Diseases

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University of Southern California
Los Angeles County Hospital
Randomized Trials in Pancreatic Diseases

- Focus acute pancreatitis
- Challenges associated pancreatitis trials
- Potential solutions
- Overview of existing randomized trials for acute pancreatitis
- Future needs and strategies
Challenges: Enrollment

Have a PANCREATITIS patient?
CALL (213) 919-PANC 24/7 LAC+USC pancreas study team
Or in numbers: (213) 919-7262
Enrollment

**Aggressive Arm**

1) Bolus LR 20cc/kg over 30 min then
2) LR @ rate 3cc/kg/hr

Hematocrit, Creatinine, BUN

Labs Increase or Labs Unchanged, Develop SIRS

Labs Decrease, No SIRS

**Time 0 hr**

**Time 12(±/- 4 hrs)**

1) Bolus LR 20cc/kg over 30 min then
2) LR @ rate 3cc/kg/hr

**Moderate Arm**

1) Bolus LR 10cc/kg over 30 min then
2) LR @ rate 1.5cc/kg/hr

Hematocrit, Creatinine, BUN

Labs Increase or Labs Unchanged, Develop SIRS

Labs Decrease, No SIRS

LR @ rate 1.5cc/kg/hr Advance diet

Buxbaum, Am J Gastroenterol 2017; 112: 797-803
Enrollment

- Pancreatitis is managed by emergency physicians, internist, surgeons, and gastroenterologist
- Multidisciplinary team is critical

Early Aggressive Hydration for Acute Pancreatitis Hastens Clinical Improvement

1James Buxbaum, 1Michael Quezada, 1Ben Da, 1Niraj Jani, Christianne Lane, 1Didi Mwengela, 1Tom Kelly, 3Paul Jhun, 4Kiran Dhanireddy, 5Loren Laine

1Division of Gastroenterology, Departments of 2Preventive Medicine, 3Surgery, 4Emergency Medicine. University of Southern California, Keck School of Medicine, Los Angeles, CA
Enrollment

- Automatic alert system increases enrollment
  - Auto-generated page, email, or text from clinical laboratory
  - Minimizes “human factor”
  - Clinical alerts generated by electronic medical record system (EMR)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Fluids RCT in AP LAC+ USC</th>
<th>Prospective Cohort in AP LAC+USC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study pager</td>
<td>Buxbaum et al</td>
<td>Chong et al</td>
</tr>
<tr>
<td>Time period</td>
<td>2013-2015 24 months</td>
<td>2015-2017 24 months</td>
</tr>
<tr>
<td>Acute pancreatitis patients identified</td>
<td>198</td>
<td>478</td>
</tr>
</tbody>
</table>

Buxbaum, Am J Gastroenterol 2017; 112: 797-803, Chong, Am J Gastroenterol (abstract) 2017
Automated Early Response System

- Automated ER pager system
- Triggered by elevated pancreatic enzymes
- Suggested risk stratification and goal directed fluid therapy
- Decreased length of hospitalization
  - Overall 6.7 to 4.6 days
  - Moderate-Severe 14.5 to 7.0

Enrollment

- 1990-2015 high quality randomized trials
  - 61 acute pancreatitis
  - 85 post ERCP pancreatitis prevention
- PEP trials, principal investigators are Gastroenterologists and candidates undergo a gastroenterology evaluation

**PANCREAS, BILIARY TRACT, AND LIVER**

Aggressive Hydration With Lactated Ringers Solution Reduces Pancreatitis After Endoscopic Retrograde Cholangiopancreatography

James Buxbaum, Arthur Yan, Kelvin Yeh, Christianne Lane, Nancy Nguyen, and Loren Laine

<table>
<thead>
<tr>
<th></th>
<th>RCT</th>
<th>Post ERCP and LR</th>
<th>Acute Pancreatitis and LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of annual potential candidates</td>
<td>135</td>
<td>140</td>
<td></td>
</tr>
<tr>
<td>Time to reach N=60</td>
<td>9 months</td>
<td>31 months</td>
<td></td>
</tr>
</tbody>
</table>

Enrollment

• Pancreatitis service
  – Residents and fellows from medicine, surgical, gastroenterology
  – Rotating attending from the various services

• Benefits
  – Cutting edge clinical care and research platform

• Model
  – Liver transplant services
  – Combined medicine, surgery, pharmacy, social work team

Challenges: Endpoint Definition
## Endpoint Definition

<table>
<thead>
<tr>
<th>Clinical Improvement within 36 hours</th>
<th>Aggressive Hydration (N=27)</th>
<th>Moderation Hydration (N=33)</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median (IQR)</strong></td>
<td>20.5 (10)</td>
<td>28.3 (15.5)</td>
<td>7.0 (1.8-27.8)</td>
</tr>
<tr>
<td><strong>N (%)</strong></td>
<td>3 (11.1)</td>
<td>12 (36.4)</td>
<td>0.08 (0.01-0.49)</td>
</tr>
</tbody>
</table>

**CLINICAL IMPROVEMENT**-composite outcome of decreased pain (visual analogue scale, tolerance of oral nutrition, decrease BUN, hematocrit, and creatinine
## Endpoint Definition

<table>
<thead>
<tr>
<th></th>
<th>Aggressive Hydration (N=27)</th>
<th>Moderation Hydration (N=33)</th>
<th>Adjusted OR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Improvement within 36 hours</strong></td>
<td>20.5 (10)</td>
<td>28.3 (15.5)</td>
<td>7.0 (1.8-27.8)</td>
</tr>
<tr>
<td><strong>Develop Hemoconcentration</strong></td>
<td>3 (11.1)</td>
<td>12 (36.4)</td>
<td>0.08 (0.01-0.49)</td>
</tr>
<tr>
<td><strong>Develop SIRS</strong></td>
<td>4 (14.8)</td>
<td>9 (27.3)</td>
<td>0.14 (0.02-0.92)</td>
</tr>
<tr>
<td><strong>Severe Pancreatitis</strong></td>
<td>0</td>
<td>1 (3.0)</td>
<td></td>
</tr>
</tbody>
</table>

Buxbaum, Am J Gastroenterol 2017; 112: 797-803
## Endpoints for Pancreatitis Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Topic</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besselink, Lancet, 2008</td>
<td>Probiotic prophylaxis</td>
<td>Composite: infected pancreatic necrosis, bacteremia, pneumonia, urosepsis, infected ascites</td>
</tr>
<tr>
<td>Bakker, JAMA, 2012</td>
<td>Necrosis management</td>
<td>Serum IL-6 level (post-procedure)</td>
</tr>
<tr>
<td>Vege, Gastroenterology, 2015</td>
<td>Pentoxifylline</td>
<td>Change in CRP, IL-6, IL-8, TNF-α levels</td>
</tr>
</tbody>
</table>
Endpoints

• Important clinical endpoints
  – death, development of severe pancreatitis
    • fortunately rare

• Design of smaller clinical trials difficult
  – required for new therapeutic approaches difficult
  – very large sample sizes needed
  – limited federal grant or pharmaceutical funding even for small studies
Pancreatitis Activity Scoring System

- Pancreatitis Activity Scoring System
  - Quantitative measurement of activity
  - Modified Delphi process
  - Encouraging results
    - cohort studies
    - not yet used in randomized trial

Parameter weights

- Organ failure* × 100 for each system
- SIRS × 25 for each criteria
- Abdominal pain (0–10) × 5
- Morphine equivalent dose (mg) × 5
- Tolerating solid diet (yes=0, no=1) × 40

Organ failure definition:
  * Modified Marshall or SOFA score ≥ 2 pts any category

Wu, Am J Gastroenterol 2017; epub ahead of print
Blinding

• High risk of bias
  – subjective components (i.e. pain)
  – composite endpoints

• PASS
  – Abdominal pain (5 per 0-10 pain score)

• Post ERCP Pancreatitis (Consensus Criterion)
  • New onset upper abdominal pain
  • Amylase>3X normal at >24 hours after procedure
  • Admission or prolongation of hospitalization >2 nights

Somatostatin to prevent post-ERCP pancreatitis

- Meta-analysis single blinded trials (n=646)
  - somatostatin prevents post ERCP pancreatitis

- Prompted large double blind randomized trial (n=746)
  - Study physicians uninvolved in ERCP
  - No benefit

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Somatostatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>395</td>
<td>351</td>
</tr>
<tr>
<td>PEP N(%)</td>
<td>19 (4.8%)</td>
<td>22 (6.3%)</td>
</tr>
</tbody>
</table>

External Validity

• Small single center studies may not be clinically applicable to other centers
  – Aggressive hydration for AP study
    • Average age was 45 years
    • No volume overload may reflect younger population rather than safety

• Selection of specific disease severity
  – Aggressive hydration for AP
    • Patients with severe pancreatitis and systemic inflammatory response syndrome were excluded
    • Results may not apply to more severe disease

Buxbaum, Am J Gastroenterol 2017; 112: 797-803
# Eligibility Criterion

<table>
<thead>
<tr>
<th>Author</th>
<th>Topic</th>
<th>Inclusion Criterion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson, Gut 2001</td>
<td>Platelet Activating Factor Inhibitor</td>
<td>Predicted Severe APACHE II &gt;6</td>
</tr>
<tr>
<td>Isenmann, Gastroenterology 2004</td>
<td>Antibiotic Prophylaxis</td>
<td>Predicted Severe: CRPmg/L &gt;150 or necrosis</td>
</tr>
<tr>
<td>Eckerwall, Annals of Surgery 2006</td>
<td>Early nasogastric feeding</td>
<td>Predicted Severe: APACHE&gt;8 or peripancreatic liquid on CT</td>
</tr>
<tr>
<td>Vege, Gastroenterology, 2015</td>
<td>Pentoxifylline</td>
<td>Predicted Severe: one of the following age&gt;60, BMI&gt;30, APACHE ≥8, hematocrit&gt;45, SIRS score&gt;2, abnormal chest radiograph, CT scan with necrosis &gt;30 gland, Balthazar grade D or E</td>
</tr>
</tbody>
</table>
External Validity

• Categories such as “predicted severe” have variable interpretations
  – Standardized quantitative activity score applicable at various times (i.e. PASS score) may be more useful

• Inclusion of patients with variable disease states clinically useful
  – Broader eligibility criterion
  – Large sample sizes
    • sub-analysis of those with mild, moderately severe, and severe pancreatitis
  – Multiple centers with diverse patient populations of different ages, ethnicities, and etiologies of pancreatitis
### Needs: Pancreatitis Randomized Trials

<table>
<thead>
<tr>
<th>Major Topic</th>
<th>Number of Randomized Controlled Trials</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic Antibiotics</td>
<td>Multiple high quality RCT (n=18)</td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>Multiple consistent (n=8) high quality RCT</td>
<td></td>
</tr>
<tr>
<td>Probiotics</td>
<td>High quality RCT (n=5)</td>
<td></td>
</tr>
<tr>
<td>Necrosis management</td>
<td>Several high quality RCT’s</td>
<td></td>
</tr>
<tr>
<td>Fluid Rate and Type</td>
<td>Few trials, mixed results and quality</td>
<td></td>
</tr>
<tr>
<td>Pharmacologic Therapy (anti-inflammatory, anti-secretory)</td>
<td>Overall low quality, with higher quality studies showing no impact of available therapy</td>
<td></td>
</tr>
</tbody>
</table>
Prophylactic Antibiotics versus Placebo for Necrotizing Pancreatitis

- >30% necrosis on computed tomography
- Multi-centered (32 sites on 2 continents)
- Randomized to early meropenem or placebo for 7-21 days
- Primary outcome of pancreatic or peripancreatic infection
- Double-blinded

<table>
<thead>
<tr>
<th></th>
<th>Meropenem</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>Pancreatic or peri-pancreatic infection</td>
<td>9 (18%)</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>10 (20%)</td>
<td>9 (18%)</td>
</tr>
<tr>
<td>Surgical intervention</td>
<td>13 (26%)</td>
<td>10 (20%)</td>
</tr>
</tbody>
</table>

Dellinger, Annals of Surgery; 245(5): 674-682
### Analysis 1.2. Comparison 1 Antibiotics versus control, Outcome 2 Infected Pancreatic Necrosis.

Review: Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Antibiotics n/N</th>
<th>Control n/N</th>
<th>Risk Ratio M-H,Random,95% CI</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pederzoli 1993</td>
<td>5/41</td>
<td>10/33</td>
<td></td>
<td>14.2%</td>
</tr>
<tr>
<td>Sainio 1995</td>
<td>9/30</td>
<td>12/30</td>
<td></td>
<td>24.3%</td>
</tr>
<tr>
<td>Schwarz 1997</td>
<td>8/13</td>
<td>7/13</td>
<td></td>
<td>26.5%</td>
</tr>
<tr>
<td>Nordback 2001</td>
<td>1/25</td>
<td>6/33</td>
<td></td>
<td>3.6%</td>
</tr>
<tr>
<td>Isenmann 2004</td>
<td>7/41</td>
<td>5/35</td>
<td></td>
<td>12.3%</td>
</tr>
<tr>
<td>Dellinger 2007</td>
<td>8/41</td>
<td>5/41</td>
<td></td>
<td>12.8%</td>
</tr>
<tr>
<td>R. Kke 2007</td>
<td>2/12</td>
<td>4/16</td>
<td></td>
<td>6.3%</td>
</tr>
</tbody>
</table>

**Total (95% CI)**

203

201

100.0 %

0.85 [0.57, 1.26]

Total events: 40 (Antibiotics), 49 (Control)

Heterogeneity: Tau² = 0.04; Chi² = 6.94, df = 6 (P = 0.33); I² = 13%

Test for overall effect: Z = 0.80 (P = 0.42)

“Nil by Mouth”/TPN

Enteral versus Parenteral Nutrition for Severe Pancreatitis

• Severe pancreatitis Apache II >8 (n=70) randomized to TPN versus enteral feeding via NJ tube for minimum 7 days
• Overall 32% patients documented infections
  – Polymicrobial (Escherichia coli and Pseudomonas aeruginosa, other gut flora

<table>
<thead>
<tr>
<th></th>
<th>Enteral</th>
<th>TPN</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Pancreatic Infection</td>
<td>20%</td>
<td>47%</td>
</tr>
<tr>
<td>Multi-organ failure</td>
<td>31%</td>
<td>79%</td>
</tr>
<tr>
<td>Mortality</td>
<td>6%</td>
<td>35%</td>
</tr>
</tbody>
</table>

Petrov, Dig Surg 2006; 23: 336-345
SEVERE PANCREATITIS

**Fluid Type**

- **Wu et al**
  - Randomized 40 patient with acute pancreatitis to lactated ringers versus normal saline
  - Outcome: Systemic Inflammatory Response Syndrome (SIRS) reduction at 24 hours

- **De Madaria et al**
  - Randomized 40 patient with acute pancreatitis to lactated ringers versus normal saline
  - Similar design but double blinded

- **Need for larger studies at multiple centers with double blind design**

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<table>
<thead>
<tr>
<th></th>
<th>WU 2014 Lactated Ringer’s</th>
<th>WU 2014 Normal Saline</th>
<th>deMadaria 2017 Lactated Ringer’s</th>
<th>deMadaria 2017 Normal Saline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SIRS 0 hours (%)</strong></td>
<td>32</td>
<td>19</td>
<td>47</td>
<td>67</td>
</tr>
<tr>
<td><strong>SIRS 24hr (%)</strong></td>
<td>5</td>
<td>19</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td><strong>SIRS 48hr (%)</strong></td>
<td>--</td>
<td>--</td>
<td>16</td>
<td>43</td>
</tr>
<tr>
<td><strong>SIRS 72hr (%)</strong></td>
<td>--</td>
<td>--</td>
<td>16</td>
<td>33</td>
</tr>
</tbody>
</table>

Fluid Rate

- Mao et al
  - Severe pancreatitis (n=76)
  - Controlled expansion
    • Less ventilator support (65% versus 94%)
    • Lower mortality (90% versus 69.4%) for controlled expansion
  
- Buxbaum et al
  - Mild pancreatitis (n=60)
  - Aggressive hydration
    • Greater clinical improvement at 36 hours (70% versus 42%)
    • Less persistent SIRS 7.4% versus 21%) with aggressive hydration

- Double blinded, multicenter studies
- Need for standard endpoints
- Need to enroll patients of variable severity (broader eligibility criterion) to improve external validity

<table>
<thead>
<tr>
<th></th>
<th>Mao et al</th>
<th>Rapid Expansion</th>
<th>Controlled Expansion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td>10-15 cc/kg/hr</td>
<td>5-10 cc/kg/hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>i.e. 1000cc/hr</td>
<td>i.e. 400cc/hr</td>
<td></td>
</tr>
<tr>
<td>Buxbaum et al</td>
<td>Aggressive Hydration</td>
<td>Standard Hydration</td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>3 cc/kg/hr</td>
<td>1.5 cc/kg/hr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>i.e. 240cc/hr</td>
<td>i.e. 120cc/hr</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacologic Therapy

Number of Randomized Trials

Lexipafant
Probiotics
Antioxidants
Gabexate
Glucagon
Apoprotinin
Octreotide
Somatostatin

Additional Trials: NSAIDs (n=2), calcitonin (n=2), cimetidine (n=2), uhnistatin (n=2), thymosin (n=1) activated protein C (n=1), iniprol (n=1).
Lexipafant

- Platelet activating factor (PAR)
  - Amplifies systemic inflammatory response syndrome
  - Prior small randomized trials indicated benefit of lexipafant, a PAR inhibitor, in severe pancreatitis
- Multicenter randomized double blinded British study of 370 (18 centers) patients with APACHE>6

<table>
<thead>
<tr>
<th></th>
<th>Lexipafant</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ Failure</td>
<td>57%</td>
<td>58%</td>
</tr>
<tr>
<td>Local complications</td>
<td>20%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Johnson, Gut 2001; 48: 62-69
Octreotide

- Octreotide decreases exocrine pancreatic secretion
- Unblinded small RCT’s suggested benefit at variable doses
- Multicenter randomized double blind German study of 302 patients (32 centers) with severe pancreatitis

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Octreotide 100ug</th>
<th>Octreotide 200ug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>16%</td>
<td>15%</td>
<td>12%</td>
</tr>
<tr>
<td>New Complication</td>
<td>71%</td>
<td>76%</td>
<td>72%</td>
</tr>
<tr>
<td>Days in Hospital (median)</td>
<td>21</td>
<td>22</td>
<td>21</td>
</tr>
</tbody>
</table>

Uhl, Gut 1999; 45: 97-104
Pharmacologic

• Cochrane Review
  – “Very Low Quality Evidence”
  – “We did not find consistent clinical benefits with any interventions”

• Low quality studies suggest benefit → refuted by very high quality double blind trials
Pharmacologic (and fluids)

• Timing of pancreatitis
  – over first 72 hours patients may transition among severity categories

• Focus of most trials on severe pancreatitis
  – 72-96 hours most damage may be done
    • Nutrition and infections still a concern but have been well studied
      – Limited information on studies during initial period

• Early enrollment is useful for clinicians needing to make decisions on presentation
Randomized Trials in Pancreatitis

• ENROLLMENT
  – Multidisciplinary team and automated mechanisms to capture all patients with pancreatitis
  – Allows very early enrollment
  – Favors larger sample size

• ENPOINTS
  – Use of validated, clinically meaningful measures
    • PASS score encouraging
  – Composite endpoints including pain, anorexia introduces risk of bias
    • DOUBLE BLIND is critical
Randomized Trials in Pancreatitis

• EXTERNAL VALIDITY
  – Multi-center trials needed
    • Variable populations and etiologies
  – Enrollment of all types of severity (mild, moderate, severe)
    • Sample size adequate to allow subgroup assessment
    • Early in disease course allows better applicability for clinicians

• IMMEDIATE NEED for high quality trials
  – Fluid rate and type
  – Pharmacologic therapy to treat inflammation and propagation of injury