Elevated early triglycerides linked to severe AP

Nawaz et al, AJG 2015
Sue, Pancreas 2017
Why fluid resuscitation in AP

• Maintenance of volume status in hospitalized patient

• Acute inflammatory illness: therapeutic intervention
  • Improve local tissue perfusion
  • Oxygen delivery

• Prevent complications
  • Necrosis
  • Organ failure
Microcirculation impaired in experimental severe AP
The goal of intravenous fluid resuscitation in acute pancreatitis is to adequately perfuse the pancreatic microcirculation so that pancreatic necrosis and its subsequent complications can be minimized or even prevented.

- Tim Gardner, CGH 2013
When is fluid resuscitation going to make an impact?

- 50% ICU transfers for acute pancreatitis occur within 24 hours of admission

- Organ dysfunction peaks on day 1
  - 17% day 1
  - 5% day 2
  - 1.9% day 3

Harrison, Crit Care Med 2007
Early resuscitation: reduced SIRS and OF

1985-2009, N=434 pts

Figure 1. SIRS and organ failure in early vs late resuscitation.

Warndorf et al, Clin Gastro Hep 2011
An international multicenter study of early intravenous fluid administration and outcome in acute pancreatitis

Singh et al, UEGJ 2016
Initial fluid resuscitation in ER (4 hours)

• Aggressive >1000 mL vs. <500 mL
  • Local complications: 15.9% vs. 19%, ns
  • Persistent organ failure: 4.8% vs. 7.1%, ns

Singh et al, UEGJ 2016
Fluid resuscitation based on 24 hrs

• Aggressive >4.3L vs. <3.2L

  • Local complications: 25.4% vs. 11.5%, p<0.025

  • Persistent organ failure: 6.2% vs. 4.2%, ns

<table>
<thead>
<tr>
<th>Acute fluid collection</th>
<th>Pancreatic necrosis</th>
<th>Extra-pancreatic necrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.7%</td>
<td>3.6%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

Singh et al, UEGJ 2016
<table>
<thead>
<tr>
<th>How to administer iv fluids?</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAP/APA practice guideline (2012)</td>
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<tr>
<td>ACG guideline (2013)</td>
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<td>AGA guideline (2007)</td>
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</table>
## Observational studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design Type</th>
<th>n</th>
<th>Aggressive Criteria</th>
<th>Non-aggressive Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>De-Madaria</td>
<td>Prospective cohort</td>
<td>247</td>
<td>Aggressive &gt;4.1L first 24 hrs</td>
<td>Moderate 3.1-4.1L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Non-aggressive &lt;3.1L</td>
<td></td>
</tr>
<tr>
<td>Warndorf</td>
<td>Retrospective cohort</td>
<td>434</td>
<td>Aggressive&gt;1/3 total in first 24 hrs</td>
<td></td>
</tr>
<tr>
<td>Wall</td>
<td>Case series</td>
<td>286</td>
<td>1998 (non-aggressive): 188mL/hr x 12 hrs</td>
<td>2008 (aggressive): 221 ml/h x 12 hrs</td>
</tr>
<tr>
<td>Muddana</td>
<td>Prospective case-control</td>
<td>129</td>
<td>4.3L first 24 hrs, then 3.9 L next 24 hrs</td>
<td></td>
</tr>
<tr>
<td>Gardner</td>
<td>Retrospective cohort</td>
<td>45</td>
<td>Aggressive&gt;1/3 total in first 24 hrs</td>
<td>Nonaggressive:&lt;1/3 total in first 24 hrs</td>
</tr>
<tr>
<td>Eckerwall</td>
<td>Case series</td>
<td>99</td>
<td>Aggressive:&gt;4L first 24 hrs</td>
<td>Non-aggressive: &lt;4L first 24 hrs</td>
</tr>
</tbody>
</table>

Adapted from Haydock et al, Ann Surgery 2013
## Randomized-controlled trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>N</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mao</td>
<td>RCT</td>
<td>115</td>
<td>Aggressive: goal hct&lt;0.35 (10.6L) in 48 hrs Nonaggressive: goal HCT≥0.35 (8.7L)</td>
</tr>
<tr>
<td>Wu</td>
<td>RCT</td>
<td>40</td>
<td>Goal-directed: 20 mL/kg bolus + 3 mL/kg/hr vs. 1.5 mL/kg/hr vs. physician-directed</td>
</tr>
<tr>
<td>Buxbaum</td>
<td>RCT</td>
<td>60</td>
<td>Aggressive: 20 mL/kg bolus + 3 mL/kg/hr Nonaggressive: 10 mL/kg bolus + 1.5 mL/kg/hr</td>
</tr>
</tbody>
</table>
Rapid hemodilution in AP

• N=115
• AP patients with APACHE>8 and admission hct≥44%
• Outcome: sepsis, mortality

Rapid hemodilution: target hct<35% by 48 hrs

Slow or standard resuscitation: target hct≥35% by 48 hrs

Mao et al, Chin Med J 2010
Rapid hemodilution: increased sepsis and mortality

• Fluids given
  • 0-24 hrs: rapid 4.8L vs 3.9L (p=0.005)
  • 24-48 hrs: rapid 5.8L vs. 4.8L (p=0.01)

• Outcomes
  • Sepsis: rapid 78.6% vs 57.6% (p=0.016)
  • Mortality: rapid 33.9% vs 15.3% (p=0.02)

Mao et al, Chin Med J 2010
Goal-directed +/- Lactated Ringer vs. saline

N=40
All eligible AP patients
Outcome: SIRS at 24 hrs

Randomize:
A. Goal-directed, Lactated Ringer’s
B. Goal-directed, Normal Saline
C. Standard, Lactated Ringer’s
D. Standard, Normal Saline

Standard Resuscitation: Judgment of treating physician
Goal-directed Resuscitation: Protocol by study investigators

Wu et al, Clin Gastro Hep 2011
Volume of Resuscitation: n=40
Similar between Goal-directed and Standard

Wu et al, Clin Gastro Hep 2011
LR reduced SIRS at 24 hours

Two-way anova
Early aggressive vs. standard (with LR)

N=60
Excluded patients with SIRS, necrosis or OF
Outcome: decrease hct, BUN, cr, pain and po intake

20 mL/kg bolus + 3 mL/kg/hr

10 mL/kg bolus + 1.5 mL/kg/hr

20 mL/kg bolus + 3 mL/kg/hr

No bolus + 1.5 mL/kg/hr

Checkpoint 1

Buxbaum et al, AJG 2017
Summary from RCTs

• Small sample sizes
• Heterogeneous populations
• Varying resuscitation protocols
• Different clinical endpoints
• **What** is optimal fluid resuscitation?

• **When** is it most effective?

• **Who** needs it?

• **How** do we move forward?
“Bellamy curve”

Intravenous Fluid volume

Complications

Optimal

Bellamy MC, Br J Anaesth 2006
Distinct profiles of disease activity

Pancreatitis Activity Score

Wu et al, AJG 2017
Resuscitation in Acute Pancreatitis Trial: RAPTor

Multi-center randomized clinical trial

- Intervention
  - aggressive vs. conservative +/- hemodynamic monitoring
  - Validate RL vs. NS
- Define the outcome
  - Complications
  - Natural history (PASS)
- Involve the FDA
  - Define clinical outcome assessment(s)
  - Drug development qualification program for acute pancreatitis