Acute pancreatitis

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## Management – Practice Guidelines

<table>
<thead>
<tr>
<th>Author (country)</th>
<th>Journal (year)</th>
<th>Severity prediction (within 48 hrs)</th>
<th>Pancreatic necrosis</th>
<th>Fluid therapy</th>
<th>Infected pancreatic necrosis (timing and methods)</th>
<th>Tertiary referral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chinese Society of Surgery and Association of Integrative Medicine</td>
<td><em>Chinese Crit Care Med (2007)</em></td>
<td>APACHE II ≥ 8 Ranson ≥ 3 Balthazar CT score ≥ II</td>
<td>CECT, NA</td>
<td>NA</td>
<td>Time (NA); open mainly</td>
<td>NA</td>
</tr>
<tr>
<td>IAP and AGA</td>
<td><em>Pancreatol (2013)</em></td>
<td>SIRS</td>
<td>CECT, 3-4 d, for predicted severe cases</td>
<td>Optimal</td>
<td>&gt; 4 wk; percutaneous drainage &gt; minimally invasive &gt; open; surgery, imaging and endoscopy etc.</td>
<td>Surgery, endoscopy</td>
</tr>
<tr>
<td>ACG</td>
<td><em>Am J Gastroenterol (2013)</em></td>
<td>BISAP</td>
<td>CECT or MRI, 2-3 d</td>
<td>Aggressive</td>
<td>&gt; 4 wk; percutaneous drainage &gt; minimally invasive &gt; open; surgery, imaging and endoscopy etc.</td>
<td>NA</td>
</tr>
<tr>
<td>Japanese Pancreatic Society</td>
<td><em>J Hepatobiliary Pancreat Sci (2015)</em></td>
<td>JSS</td>
<td>CECT or MRI, &lt; 1 wk</td>
<td>Aggressive</td>
<td>&gt; 4 wk; percutaneous drainage &gt; minimally invasive &gt; open; surgery, imaging and endoscopy etc.</td>
<td>Severe</td>
</tr>
<tr>
<td>Italian Pancreatology Association</td>
<td><em>Dig and Liver Dis (2016)</em></td>
<td>NA</td>
<td>CECT or MRI, &lt; 3 d</td>
<td>Aggressive</td>
<td>&gt; 4 wk; percutaneous drainage &gt; minimally invasive &gt; open; surgery, imaging and endoscopy etc.</td>
<td>NA</td>
</tr>
<tr>
<td>AGA</td>
<td><em>Gastroenterol (2018)</em></td>
<td>NA</td>
<td>NA</td>
<td>Goal-directed</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>National Institute for Health and Care Excellence (NICE)</td>
<td><em>BMJ (2018)</em></td>
<td>NA</td>
<td>NA</td>
<td>Goal-directed</td>
<td>Endoscopic drainage, if anatomically feasible</td>
<td>NA</td>
</tr>
<tr>
<td>World Society of Emergency Surgery (WSES)</td>
<td><em>World J Emerg Surg (2019)</em></td>
<td>CRP ≥ 150 mg/l BISAP</td>
<td>CECT 72–96 h, for predicted severe cases</td>
<td>Goal-directed</td>
<td>&gt; 4 wk; percutaneous drainage &gt; minimally invasive &gt; open; surgery, imaging and endoscopy etc.</td>
<td>NA</td>
</tr>
</tbody>
</table>
## AGA recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Strength of recommendation</th>
<th>Quality of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A. In patients with AP, the AGA suggests using goal-directed therapy for fluid management. <strong>Comment:</strong> The AGA makes no recommendation whether normal saline or Ringer’s lactate is used.</td>
<td>Conditional</td>
<td>Very low</td>
</tr>
<tr>
<td>1B. In patients with AP, the AGA suggests against the use of HES fluids.</td>
<td>Conditional</td>
<td>Very low</td>
</tr>
<tr>
<td>2. In patients with predicted severe AP and necrotizing AP, the AGA suggests against the use of prophylactic antibiotics.</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>3. In patients with acute biliary pancreatitis and no cholangitis, the AGA suggests against the routine use of urgent ERCP.</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>4. In patients with AP, the AGA recommends early (within 24 h) oral feeding as tolerated, rather than keeping the patient nil per os.</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>5. In patients with AP and inability to feed orally, the AGA recommends enteral rather than parenteral nutrition.</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>6. In patients with predicted severe or necrotizing pancreatitis requiring enteral tube feeding, the AGA suggest either NG or NJ route.</td>
<td>Conditional</td>
<td>Low</td>
</tr>
<tr>
<td>7. In patients with acute biliary pancreatitis, the AGA recommends cholecystectomy during the initial admission rather than after discharge.</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
<tr>
<td>8. In patients with acute alcoholic pancreatitis, the AGA recommends brief alcohol intervention during admission.</td>
<td>Strong</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
Unmet need in management

- Pharmacological therapies (for acinar cells?)
- Multiple disciplinary team & hierarchical (multi-level hospitals)
- Disease severity classification and early prediction
- Fluid therapy: Type of fluid? Rate of given? Judge fluid responsiveness?
- Specific and early organ support therapy
- Treatment of aetiology (e.g. biliary, alcohol and genetics) and co-morbidities (e.g. diabetes, fatty liver, hypertriglyceridaemia)
- Local complications (timing and methods)
Project 1 – Preclinical validation and RCTs for pathological calcium signalling inhibitors
Project 1 – Research basis

Liverpool, UCLA and Chengdu:
- **CEL inhibitor, 3-benzyl-6-chloro-2-pyrone (3-BCP)**

- **ORAI1 inhibitor, GSK-7975A and CM_128**

- **MPTP inhibitor, DEB025 and TRO40303**

- **IP₃R inhibitor, caffeine**

Other groups:
- **SOCE inhibitor pyrtriazoles**
  Riva B et al. J Med Chem 2018;61:9756-9783

- **ORAI1 inhibitor, CM4620**
  Waldron RT et al. J Physiol 2019;597:3085-3105
Project 1 – Proposed work

West China Drug Discovery Chain

- Tech training & Service
- Manufacture Circulation
- Production & Sale
- Clinical Research
- Pre-clinical Research
- Exploring & Finding

CalciMedica

Cypralis Pipeline

- Target to Lead
- Lead Optimisation
- Pre-Clinical Dev

- Liver Disease (Gilead collaboration)
- Acute Tissue Injury
- Inflammation *
- Acute Tissue Injury *

- Monkey Base, Drug Efficacy Base, GLP (CRO Platform)
- Open labs, Public Tech Platform, National Key Lab

National GCP Centre

Data & Biobanks

Farshu Ma CEO

Michael Peel CSO

Ken Stauderman CSO

Sudarshan Hebbar CMO
Project 2 – Early disease severity predictive biomarker discovery and validation
Project 2 – Research basis 1

A: Organ Failure

B: Mortality

Project 2 – Research basis 2

24 hrs, 92 Arrays
126 DE genes

Multiplex for cytokines

Circulating histones

Hierarchical Clustering

Disease Class: Mild Severe

-3.78 0.00 3.78

Nunes QM and Huang W et al. 2019 Manuscript in preparing

Deng L et al. Medicine (Baltimore) 2017;96:e7312

Liu T and Huang W et al. Br J Surg 2017;104(9):1215-1225
Project 2 – Proposed work

- Acute pancreatitis database and biobank
  - Whole blood RNA
    - NanoString
  - Clinical scores
    - Peripheral WBC predictive panel
    - BISAP, Glasgow, APACHE-II and etc.
  - Routine biomarkers
    - BUN, Cr, HCT, WBC, CRP and etc.
  - Multiple cytokines
    - TNF-α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-13, IL-17 and etc.

- Biochemistry
  - Luminex xMAP

- Sensitivity, specificity and AUC calculation from ROC
  - WBC transcriptome predictive panel > other markers
  - Predictive kit commercialised

Qing Xia
Robert Sutton

Not fully validated
Fully validated

Bioinformatics
Marched panel
Project 3 – Early fluid therapy and monitoring fluid responsiveness in acute pancreatitis
# Project 3 - Passive leg raising test

Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids?

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**Table. Summary of Diagnostic Accuracy for Hypovolemia Responsive to Fluids**

<table>
<thead>
<tr>
<th>Measures and Included Studies</th>
<th>No. of Studies</th>
<th>No. of Patients</th>
<th>Cutoff for Measures, Mean (Range)</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>Positive LR (95% CI)</th>
<th>Negative LR (95% CI)</th>
<th>Diagnostic OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Static Measure</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Central venous pressure</td>
<td>7</td>
<td>356</td>
<td>8 min Hg (6-9)</td>
<td>62 (54-69)</td>
<td>76 (50-87)</td>
<td>2.6 (1.4-4.6)</td>
<td>0.50 (0.39-0.65)</td>
<td>58 (5-11)</td>
</tr>
<tr>
<td><strong>Dynamic Measures</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse pressure variation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled ventilation, $V_i \geq 7.0 \text{ mL/kg}$</td>
<td>17</td>
<td>768</td>
<td>11 (4-15)</td>
<td>84 (75-90)</td>
<td>84 (77-90)</td>
<td>5.3 (3.5-8.1)</td>
<td>0.19 (0.12-0.30)</td>
<td>50 (13-57)</td>
</tr>
<tr>
<td>Controlled ventilation, $V_i &lt; 7.0 \text{ mL/kg}$</td>
<td>5</td>
<td>219</td>
<td>8 (5-12)</td>
<td>72 (61-81)</td>
<td>91 (83-95)</td>
<td>7.9 (4.1-16)</td>
<td>0.30 (0.21-0.44)</td>
<td>26 (11-61)</td>
</tr>
<tr>
<td>Strode volume variation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled ventilation</td>
<td>9</td>
<td>343</td>
<td>13 (10-20)</td>
<td>79 (67-87)</td>
<td>84 (74-90)</td>
<td>4.9 (2.8-8.5)</td>
<td>0.25 (0.15-0.43)</td>
<td>20 (19-73)</td>
</tr>
<tr>
<td>Spontaneous breathing</td>
<td>2</td>
<td>53</td>
<td>10-12d</td>
<td>57-100d</td>
<td>44-57d</td>
<td>1.0-2.3d</td>
<td>0.05-0.58d</td>
<td>1.43d</td>
</tr>
<tr>
<td>Inferior vena cava variation</td>
<td>4</td>
<td>137</td>
<td>15 (12-21)</td>
<td>77 (44-94)</td>
<td>85 (49-97)</td>
<td>5.3 (1.1-27)</td>
<td>0.27 (0.08-0.87)</td>
<td>71 (2-222)</td>
</tr>
<tr>
<td>Response to passive leg raising</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in cardiac output</td>
<td>17</td>
<td>788</td>
<td>11 (7-15)</td>
<td>88 (80-93)</td>
<td>62 (89-95)</td>
<td>11 (7.6-17)</td>
<td>0.13 (0.07-0.22)</td>
<td>88 (39-196)</td>
</tr>
<tr>
<td>Change in pulse pressure</td>
<td>5</td>
<td>278</td>
<td>10 (9-12)</td>
<td>62 (54-70)</td>
<td>63 (76-88)</td>
<td>3.6 (2.5-5.4)</td>
<td>0.45 (0.36-0.57)</td>
<td>8 (5-14)</td>
</tr>
<tr>
<td>Change in cardiac output following passive leg raising</td>
<td>6</td>
<td>294</td>
<td>10 (7-12)</td>
<td>92 (82-97)</td>
<td>92 (86-94)</td>
<td>11 (5.3-21)</td>
<td>0.08 (0.03-0.21)</td>
<td>139 (41-474)</td>
</tr>
<tr>
<td>Spontaneous breathing</td>
<td>5</td>
<td>181</td>
<td>12 (10-13)</td>
<td>88 (80-94)</td>
<td>88 (80-94)</td>
<td>7.0 (3.8-13.1)</td>
<td>0.22 (0.09-0.54)</td>
<td>54 (15-195)</td>
</tr>
</tbody>
</table>

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Bentzer P et al. JAMA 2016;316:1298-309
Project 3 – Proposed work

China-NZ Governmental Strategic Alliance Award

Study design

- Pts on AD
- Recruitment

- BISAP > 2 or Glasgow > 2

control

score > 2

0, 8, 16, 24 h

score < 2

- HR ≥ 120 bpm
- MAP < 65 mmHg
- UO < 0.5 ml/kg/h
- HCT > 44%

- PLRT-ΔSV > 10%
- PLRT-ΔSV < 10%

- Fluid rate 5-10 ml/kg/h
- Fluid response (+)
- Fluid rate 5-10 ml/kg/h

- Fluid rate 1.5-3 ml/kg/h
- Fluid response (-)
- Fluid rate 1.5-3 ml/kg/h

Jin T et al. 2019 Manuscript in preparing
Project 4 – Omics studies with acute pancreatitis
Project 4 – Research resources

Capacity: 10 M
Stored: 2 M

Healthy volunteers: 300,000 with serum, plasma and buffy coat: 800,000

Tumour and match blood: 200,000

Hepatitis B: 390,000

Western China geriatric cohort: 80,000

Others: 600,000

Sate Key Laboratory of Biotherapy:
Professor of genetics and bioinformatics

Project 4 – Proposed work

- SNP
- CNV
- LOH
- Genomic rearrangement
- Rare variant
- DNA methylation
- Histone modification
- Chromatin accessibility
- TF binding
- miRNA
- Gene expression
- Alternative splicing
- Long non-coding RNA
- Small RNA
- Protein expression
- Post-translational modification
- Cytokine array
- Metabolite profiling in serum, plasma, urine, CSF, etc.

Acknowledgments

- West China Pancreas Centre: Professors Qing Xia, Lihui Deng, Weimin Hu, Xubao Liu, Yan Kang, Bin Song, Yu Cao and all multiple-disciplinary members

- State Key Laboratory of Biotherapy of Sichuan University: Professors Lu Chen and Xianghui Fu; colleagues from Nanjing, Nanchang and Shanghai

- International collaborators: Professors Robert Sutton (Liverpool), John A. Windsor (Auckland), Vikesh K. Singh (Baltimore), J Enrique Dominguez-Munoz (Santiago de Compostela)

- Invitation from Professor David C. Whitcomb (Pittsburgh) and PancreasFest

- Email address: dr_wei_huang@scu.edn.cn; wechat: iPancreas