Revised JPN Guidelines for the Management of Acute Pancreatitis: JPN Guidelines 2015

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\textsuperscript{2)} Department of Surgery, Teikyo University School of Medicine, Japan
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The Japanese Guidelines for the Management of Acute Pancreatitis

English versions in 2006, 2010

4th Edition in 2015
with mobile application

(PMID: 25973947)
With the graded recommendations, where the evidence was unclear, Meta-Analysis team conducted an additional new meta-analysis in four subject areas based on randomized controlled trials.

(1) prophylactic antibiotics use
(2) prophylactic pancreatic stent placement for the prevention of post-ERCP pancreatitis
(3) prophylactic non-steroidal anti-inflammatory drugs (NSAIDs) for the prevention of post-ERCP pancreatitis
(4) peritoneal lavage
Grading the Strength of Recommendations

graded with reference to
(1) the quality of the evidence,
(2) the preferences of the patient,
(3) risks and benefit,
(4) cost estimates, etc.
With the Delphi method and nominal group technique method, \( \geq 70\% \) were approved.

Grading of Recommendations

1: Strong Recommendations; “recommend”
2: Weak Recommendations; “suggest”
Classification of Pancreatic Fluid Collection by the Revised Atlanta Classification 2012

- **APFC (sterile)**: acute peripancreatic fluid collection
- **APFC (infected)**
- **ANC (sterile)**: acute necrotic collection
- **ANC (infected)**
- **PPC (sterile)**: pancreatic pseudocyst
- **PPC (infected)**
- **WON (sterile)**: walled-off necrosis
- **WON (infected)**

4 weeks

<4 weeks after onset of pancreatitis

>4 weeks after onset of pancreatitis
Flowchart for the Management of Acute Pancreatitis

- **Diagnosis of AP**
  - Medical treatment
  - Establish the etiology
    - Biliary pancreatitis*
      - Assessment of severity
        - Mild AP
          - Medical treatment
        - Severe AP
          - Referral
            - Intensive care
              - Intra-arterial infusion therapy (option)
              - CHDF (option)
            - Infected pancreatic necrosis
              - Therapeutic intervention
            - Pancreatic abscess
              - Drainage
        - Continue Basic treatment
          - Transfer to specialized centers / units
            - Intensive care
              - Management of organ failure
              - Fluid management
              - Nutritional support
                - early enteral nutrition is recommended
              - Infection control
              - Management of ACS
                - Arterial infusion therapy (option)
                  - CHDF/CIDF (option)
              - Conservative treatment
                - in cases of suspected infection
                  - Drainage / Necrosectomy
                    - Intervention
                      - Early intervention is not recommended
                        (preferably >3 weeks after onset)
F. Fluid therapy

12. Use extracellular solution (lactated Ringer’s solution, etc.) (1C)
13. In shock or dehydration, short-time rapid fluid resuscitation (150–600mL/h) with great care to avoid excessive fluid infusion. Without dehydration, fluid infusion (130–150mL/h). (1C)
14. If MAP ≥ 65mmHg & urine output ≥0.5mL/kg/h has been secured, rapid fluid infusion should be discontinued. (2C)
Antibiotics prophylaxis
I. Antibiotics prophylaxis

(Systematic Review/Meta-analysis: 8 papers)

Severe & Necrotizing Pancreatitis: Survival/Infectious complications NO CHANGE


Prophylactic antibiotics is not recommended
## Antibiotics Prophylaxis in Severe / Necrotizing Pancreatitis

**New meta-analysis of RCT:** ABT administrated within 48h or 72h of onset  
(by meta-analysis team of JPN Guidelines 2015)

**Mortality**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotics use Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pederzoli</td>
<td>3</td>
<td>41</td>
<td>4</td>
<td>33</td>
<td>15.7%</td>
<td>0.57 [0.12, 2.76]</td>
<td>1993</td>
</tr>
<tr>
<td>Sainio</td>
<td>1</td>
<td>30</td>
<td>7</td>
<td>30</td>
<td>25.9%</td>
<td>0.11 [0.01, 0.99]</td>
<td>1995</td>
</tr>
<tr>
<td>Nordback</td>
<td>2</td>
<td>25</td>
<td>5</td>
<td>33</td>
<td>15.2%</td>
<td>0.49 [0.09, 2.75]</td>
<td>2001</td>
</tr>
<tr>
<td>Isenmann</td>
<td>3</td>
<td>41</td>
<td>4</td>
<td>35</td>
<td>15.3%</td>
<td>0.61 [0.13, 2.94]</td>
<td>2004</td>
</tr>
<tr>
<td>Rokke</td>
<td>3</td>
<td>36</td>
<td>4</td>
<td>37</td>
<td>13.8%</td>
<td>0.75 [0.16, 3.62]</td>
<td>2007</td>
</tr>
<tr>
<td>Xue</td>
<td>3</td>
<td>29</td>
<td>4</td>
<td>27</td>
<td>14.2%</td>
<td>0.66 [0.13, 3.28]</td>
<td>2009</td>
</tr>
</tbody>
</table>

Total (95% CI) 202 195 100.0% 0.48 [0.25, 0.94]

Total events 15 28

Heterogeneity: Chi² = 2.30, df = 5 (P = 0.81); I² = 0%
Test for overall effect: Z = 2.15 (P = 0.03)

**Infected pancreatic necrosis**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Antibiotics use Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pederzoli</td>
<td>5</td>
<td>41</td>
<td>10</td>
<td>33</td>
<td>24.0%</td>
<td>0.32 [0.10, 1.05]</td>
<td>1993</td>
</tr>
<tr>
<td>Sainio</td>
<td>9</td>
<td>30</td>
<td>12</td>
<td>30</td>
<td>20.7%</td>
<td>0.64 [0.22, 1.87]</td>
<td>1995</td>
</tr>
<tr>
<td>Nordback</td>
<td>1</td>
<td>25</td>
<td>6</td>
<td>33</td>
<td>12.3%</td>
<td>0.19 [0.02, 1.67]</td>
<td>2001</td>
</tr>
<tr>
<td>Isenmann</td>
<td>7</td>
<td>41</td>
<td>5</td>
<td>35</td>
<td>11.0%</td>
<td>1.24 [0.35, 4.30]</td>
<td>2004</td>
</tr>
<tr>
<td>Rokke</td>
<td>3</td>
<td>36</td>
<td>6</td>
<td>37</td>
<td>13.4%</td>
<td>0.47 [0.11, 2.04]</td>
<td>2007</td>
</tr>
<tr>
<td>Xue</td>
<td>8</td>
<td>29</td>
<td>10</td>
<td>27</td>
<td>18.5%</td>
<td>0.65 [0.21, 2.00]</td>
<td>2009</td>
</tr>
</tbody>
</table>

Total (95% CI) 33 49

Heterogeneity: Chi² = 3.54, df = 5 (P = 0.62); I² = 0%
Test for overall effect: Z = 2.29 (P = 0.02)
I. Antibiotics prophylaxis

17. Not necessary in mild pancreatitis. (1A)
   In severe pancreatitis or necrotizing pancreatitis may improve the prognosis, if carried out in the early phases of pancreatitis (within 72 h of onset). (2B)

18. No antifungal agents (1C)
19. The effectiveness of intravenous administration of protease inhibitor (gabexate mesilate) for improving prognosis and the rate of complications of acute pancreatitis has not been clearly proven. (ungraded B)

27. Continuous regional arterial infusion therapy is reported to be effective in reducing pancreatic infection and mortality rates for severe acute pancreatitis and acute necrotizing pancreatitis, but its efficacy has not been confirmed. (ungraded B)
L. Intensive care

25. No peritoneal lavage (2B)

26. For severe cases with unstable hemodynamics + anuria even after sufficient initial fluid infusion, or with abdominal compartment syndrome (ACS), CHF/CHDF should be introduced. (1C)

But, routine CHF/CHDF is not recommended. (2C)
Nutritional support
K. Nutritional support

20. In **mild** cases: **NO** hyperalimentation. (1B)

22. In severe cases: **start enteral nutrition within at least 48 h of admission**. (2A)

23. **Enteral jejunal tubes** is recommended, if impossible, use duodenum or stomach. (2B)

24. The initiation of **oral administration** should be determined using the **subsidence of abdominal pain and the serum pancreatic enzyme** (especially serum lipase) level, etc. (2B)
Prevention of post-ERCP pancreatitis
Meta-analysis of RCTs for the effects of prophylactic pancreatic stent placement on the prevention of post-ERCP pancreatitis (by the meta-analysis team of JPN Guidelines 2015)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Stent Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fazel 2003</td>
<td>2</td>
<td>40</td>
<td>10</td>
<td>36</td>
<td>8.3%</td>
<td>0.14 [0.03, 0.68]</td>
</tr>
<tr>
<td>Harewood 2005</td>
<td>1</td>
<td>11</td>
<td>2</td>
<td>8</td>
<td>1.8%</td>
<td>0.30 [0.02, 4.06]</td>
</tr>
<tr>
<td>Ito 2010</td>
<td>1</td>
<td>35</td>
<td>8</td>
<td>35</td>
<td>6.5%</td>
<td>0.10 [0.01, 0.94]</td>
</tr>
<tr>
<td>Kawaguchi 2012</td>
<td>1</td>
<td>60</td>
<td>8</td>
<td>60</td>
<td>6.5%</td>
<td>0.11 [0.01, 0.91]</td>
</tr>
<tr>
<td>Lee 2012</td>
<td>6</td>
<td>50</td>
<td>15</td>
<td>51</td>
<td>10.9%</td>
<td>0.33 [0.12, 0.93]</td>
</tr>
<tr>
<td>Pan 2011</td>
<td>4</td>
<td>20</td>
<td>14</td>
<td>20</td>
<td>9.3%</td>
<td>0.11 [0.03, 0.46]</td>
</tr>
<tr>
<td>Patel 1999</td>
<td>2</td>
<td>18</td>
<td>6</td>
<td>18</td>
<td>4.4%</td>
<td>0.25 [0.04, 1.46]</td>
</tr>
<tr>
<td>Smithline 1993</td>
<td>6</td>
<td>48</td>
<td>9</td>
<td>50</td>
<td>6.4%</td>
<td>0.65 [0.21, 1.99]</td>
</tr>
<tr>
<td>Sofuni 2007</td>
<td>3</td>
<td>98</td>
<td>14</td>
<td>103</td>
<td>11.0%</td>
<td>0.20 [0.06, 0.72]</td>
</tr>
<tr>
<td>Sofuni 2011</td>
<td>20</td>
<td>213</td>
<td>31</td>
<td>213</td>
<td>23.4%</td>
<td>0.61 [0.33, 1.11]</td>
</tr>
<tr>
<td>Taransky 1998</td>
<td>1</td>
<td>41</td>
<td>10</td>
<td>39</td>
<td>8.3%</td>
<td>0.07 [0.01, 0.60]</td>
</tr>
<tr>
<td>Tsuchiya 2007</td>
<td>1</td>
<td>32</td>
<td>4</td>
<td>32</td>
<td>3.2%</td>
<td>0.23 [0.02, 2.14]</td>
</tr>
</tbody>
</table>

Total (95% CI): 666 (665) 100.0% 0.31 [0.21, 0.44]

Total events: 48 131

Heterogeneity: Chi² = 14.11, df = 11 (P = 0.23); I² = 22%
Test for overall effect: Z = 6.53 (P < 0.00001)
Meta-analysis of RCTs for the effect of NSAIDs on the prevention of post-ERCP pancreatitis (by the meta-analysis team of JPN Guidelines 2015)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>NSAIDs</th>
<th>Placebo</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Dobronte 2013</td>
<td>11</td>
<td>130</td>
<td>11</td>
</tr>
<tr>
<td>Elmunzer 2012</td>
<td>27</td>
<td>295</td>
<td>52</td>
</tr>
<tr>
<td>Khoshbaten 2007</td>
<td>2</td>
<td>50</td>
<td>13</td>
</tr>
<tr>
<td>Montano 2007</td>
<td>4</td>
<td>75</td>
<td>12</td>
</tr>
<tr>
<td>Murray 2003</td>
<td>7</td>
<td>110</td>
<td>17</td>
</tr>
<tr>
<td>Otsuka 2012</td>
<td>2</td>
<td>51</td>
<td>10</td>
</tr>
<tr>
<td>Sotoudehmanesh 2007</td>
<td>7</td>
<td>245</td>
<td>15</td>
</tr>
</tbody>
</table>

Total (95% CI)

- Total: 956
- Placebo: 938
- 100.0%
- Odds Ratio: 0.41 [0.30, 0.57]

Total events: 60, 130
Heterogeneity: Chi² = 6.14, df = 6 (P = 0.41); I² = 2%
Test for overall effect: Z = 5.37 (P < 0.00001)
P. Prevention of post-ERCP pancreatitis

37. Prophylactic temporary pancreatic stent placement is recommended for the prevention of post-ERCP pancreatitis in the high-risk groups. (2A)

The guidewire method is very likely to reduce the incidence of post-ERCP pancreatitis. (2A)

38. For the prevention of post-ERCP pancreatitis, the intrarectal administration of NSAIDs should be carried out for all cases undergoing ERCP with no contraindications. (2A)

(Other drugs should not be used as routine preventive measures.)
Interventions for the local complications
33. For necrotizing pancreatitis, conservative treatment at first. Intervention is applied to cases of infected pancreatic necrosis with an aggravated general condition. (1C)

34. Routine use of FNA is not required, and clinical signs and CT should be used for a comprehensive determination. If an aggravated general condition is observed, percutaneous or endoscopic drainage should be given for diagnosis and treatment. (1C)

35. If possible, intervention for infected pancreatic necrosis should be performed after 4 weeks of onset, when the necrosis has been sufficiently walled off (WON period). (2C)
1. Repeat severity assessments at diagnosis, within 24 h, and 24–48 h after diagnosis based on the JPN Severity Score (JSS).

2. In severe pancreatitis, transfer to an appropriate medical facility should be considered within 3 h after diagnosis.

3. Causes of pancreatitis should be differentiated within 3 h.

4. For gallstone-induced pancreatitis, early ERC + ES should be considered in patients with cholangitis and/or prolonged passage disorder of the biliary tract with jaundice.

5. At a medical facility for severe cases, abdominal enhanced CT should be performed within 3 h. A non-enhanced area and the extent of the disease should be examined, and severity should be assessed on the basis of the CT Grades.
6. Fluid replacement and monitoring within 48 h of onset, MAP $\geq$ 65 mmHg and urinary output $\geq$ 0.5 ml/kg/h.

7. Pain control should be provided.

8. Prophylactic wide-spectrum antibiotics for severe acute pancreatitis within 72 h of onset.

9. Even if without peristalsis, enteral nutrition should be started (jejunal administration is desirable) within 48 h of diagnosis.

10. Cholecystectomy should be performed after the subsiding of symptoms of pancreatitis for gallstone-induced pancreatitis.
Rapid Communication

Acute pancreatitis bundles: 10 clinical regulations for the early management of patients with severe acute pancreatitis in Japan

Morihisa Hirota · Toshihiko Mayumi · Tooru Shimossegawa

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Keywords: Acute pancreatitis · Bundle · Fluid therapy · Initial therapy · Severe acute pancreatitis

Acute pancreatitis (AP) is an inflammatory disease of diverse severity. Early management is indispensable to cure patients with AP, especially those who show symptoms of severe AP (SAP) [1–3]. The mortality from sepsis, which is another fatal disease, has been improved by the establishment and implementation of guidelines for the early man-

Table I  Pancreatitis bundles [5]

1. When a diagnosis of acute pancreatitis has been made, repeated severity assessment should be carried out within 24 h, and 24–48 h after diagnosis on the basis of estimating the severity assessment criteria of acute pancreatitis prepared by the Ministry of Health, Labour and Welfare.
2. For patients with severe acute pancreatitis, transference to an appropriate medical facility should be considered within 3 h after a diagnosis has been made.
3. For patients with acute pancreatitis, causes of pancreatitis should be differentiated using medical records, hematological and biochemical examination, and imaging and endoscopic examinations.
6. Sufficient amount of fluid replacement and monitoring should be performed, and MAP should be maintained > 65 mmHg and urinary output > 0.5 ml/kg/h, respectively.

**Table 2** Summary of the rates of valid answers on the questionnaire and the implementation of each statement of the pancreatitis bundles and the mortality

<table>
<thead>
<tr>
<th>Statement no.</th>
<th>Achievement</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ 8 items</td>
<td>7.6%*</td>
</tr>
<tr>
<td></td>
<td>&lt; 8 items</td>
<td>13.7%</td>
</tr>
</tbody>
</table>

(*P = 0.042)
Q. Clinical indicators (Pancreatitis Bundles 2015)

39. A high rate of implementation of the pancreatitis bundles may contribute to improving prognosis of patients with severe acute pancreatitis. (1C)
Mobile Application for Acute Pancreatitis Guidelines
Mobile Application for Acute Pancreatitis Guidelines
In severe pancreatitis, antibiotics prophylaxis within 72 hrs on onset.

In severe cases: start enteral nutrition within at least 48 hrs of admission

Prevention of post-ERCP pancreatitis with stent & NSAIDs

Interventions for the local complications

Follow pancreatitis bundles

Mobile application → distribution, assessment

We need your feedback