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ORIGINAL ARTICLE

Revised Japanese guidelines for the management of acute pancreatitis 2015: revised concepts and updated points

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Abstract
Background Taking together the recent dramatic changes of the revised Atlanta classification and evidence newly obtained such as the role of step-up approach for necrotizing pancreatitis, the revision committee of the Japanese (JPN) Guidelines 2015 was prompted to perform an extensive revision of the guidelines.
Methods The JPN Guidelines 2015 was compared to the former edition 2010, and revision concepts and major revision points were reviewed. We compared the JPN 2015 with the other two guidelines, International Association of Pancreatology (IAP)/American Pancreas Association (APA) 2013 and American College of Gastroenterology (ACG) 2013, in order to clarify the distinct points.
Results The meta-analysis team conducted a new meta-analysis of four subjects that have been associated with conflicting results. It is apparent that the revised guidelines have been created more systematically and more objectively. As of antibiotics prophylaxis, its use in early phase (within 72 h of onset) for severe acute pancreatitis is recommended in JPN 2015 according to the results of original meta-analysis, whereas the other two guidelines do not recommend its routine use. An approach and management of local complications in necrotizing pancreatitis including infected necrosis are almost similar in the three guidelines. JPN 2015 alone emphasizes the implementation of the pancreatitis bundles that specify the management and treatment within the first 48 h after the onset of severe acute pancreatitis.
Conclusion The JPN Guidelines 2015 prove to be the highest quality in terms of systematic literature review conducting original analyses by the meta-analysis team, determining the grading of recommendations and providing pancreatitis bundles.

Keywords Enteral nutrition · Pancreatitis bundles · Post-endoscopic retrograde cholangiopancreatography pancreatitis · Prophylactic antibiotics · Therapeutic intervention

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Introduction

Acute pancreatitis is one of the most common gastrointestinal disorders which require acute hospitalization, and there is a global trend toward an increased incidence of the disease, being a reported incidence 5–80 cases per 100,000 persons per year [1, 2]. According to a national survey in Japan conducted by the Intractable Pancreatic Disease Investigation and Research Group (IPDIRG) of the Japanese Ministry of

Health, Labour and Welfare, the number of acute pancreatitis patients was estimated to be 63,080/year in 2011 [3], which was significantly higher than 19,500/year in 1998 [2]. The incidence of severe acute pancreatitis is around 20% in recent years in Japan, and therefore this common disease associated with mortality up to 10 to 30% in severe cases requires up-to-date evidence-based guidelines for its management.

A recent systematic review for the 30 guidelines for acute pancreatitis including JPN Guidelines 2006 [2, 4–11] published since 1988, which was conducted to determine the quality of guidelines, has highlighted the need for a high quality update and selected JPN Guidelines as one of the four most up-to-date guidelines with high quality scores [12]. JPN Guidelines 2006 had been revised in 2010, incorporating a new severity scoring system defined by IPDIRG and employing pancreatitis bundles as clinical indicators. Meanwhile, since the Atlanta classification was first established in 1992 [13], major revision in the definitions and classification of AP was made in 2012 [14]. Local complications are newly defined as peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocysts, and walled-off necrosis (sterile or infected). Isolated extrapancreatic necrosis is also included under the term necrotizing pancreatitis. Furthermore, recent advances in minimally invasive approach for these local complications have accumulated new evidence for the management of acute pancreatitis. Taking these recent changes and newly obtained evidence together, the revision committee of JPN Guidelines 2015 published a new version [15], and the English edition based on this new version is now available in this journal [16].

In this article, we describe major revision points in JPN Guidelines 2015 from the previous version, and examine distinct points in comparison with recent high quality guidelines of the International Association of Pancreatology (IAP)/American Pancreas Association (APA) evidence-based guidelines for the management of acute pancreatitis [17] and the American College of Gastroenterology (ACG) guideline for the management of acute pancreatitis [18].

Materials and methods

The JPN Guidelines 2015 was compared to the former edition of guidelines 2010 [19–29], and revision concepts and major revision points were reviewed. Furthermore, we compared the JPN Guidelines 2015 with the other two guidelines, IAP/APA Evidence-based Guidelines 2013 [17] and ACG Guideline 2013 [18], both of which were previously ranked as the four most up-to-date guidelines with high quality scores [12], in order to clarify the distinct points.

Results and discussion

Comparison between guidelines 2015 and 2010

1) Quality of evidence and grading the strength of recommendations

In the previous version, the evidence obtained from each reference item was evaluated in accordance with the method of scientific classification used at the Cochrane Library (March, 2009) [19], and the quality of evidence for each parameter associated with the diagnosis and treatment of acute pancreatitis was determined. Based on the results obtained from these procedures, recommendation grades of A–D were determined according to the definitions by the Minds Manual for Preparation of Management Guidelines (2007 edition) [30] (Table 1). In the JPN Guidelines 2015 [16], systematic literature review was made by a step-by-step method: (1) extraction of risk/benefit outcomes from the clinical question (SCOPE); (2) evaluation of each paper according to the study design, and assessment of the presence/absence of factors that decrease or increase evidence levels, and finally a comprehensive evaluation of the evidence (body of evidence) was graded from Grades A (high), B (moderate), C (low) and D (very low) using the GRADE system [31]. Furthermore, the strength of recommendations was graded according to the quality of evidence, the patient preference, risk and benefit, and cost, etc. In terms of consensus-building, a vote by the member of committee was taken using the Delphi method and a nominal group technique method, and issues with a support rate of more than 70% were approved. The grading of

Table 1 Grades of recommendation being adopted in the JPN Guidelines 2010

Grade of recommendation	Contents
A	Recommended strongly to perform
	Evidence is strong and clear clinical effectiveness can be expected
B	Recommended to perform
	Evidence is moderate or strong, although evidence of effectiveness is sparse
C1	Evidence is sparse, but may be considered to perform
	Effectiveness can possibly be expected
C2	Scientific evidence is not sufficient, so clear recommendation cannot be made
	Evidence is not sufficient to support or deny effectiveness
D	Considered to be unacceptable
	There is evidence to deny effectiveness (to show harm)

recommendations was divided into the two categories: strong recommendation: (1) and weak recommendation (2); and recommendations and quality of evidence were described like 1A, 1B, 2B and 1C. The meta-analysis team (four members) for JPN Guidelines 2015 conducted a new meta-analysis of four subjects that have been associated with conflicting results. Consequently, it is apparent that the revised guidelines have been created more systematically and more objectively.

2) Meta-analysis

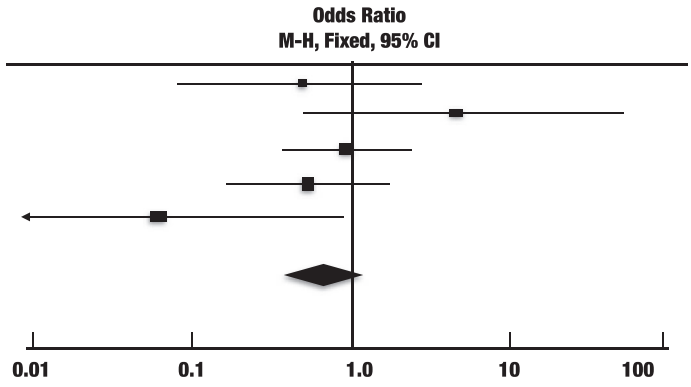
According to a recent meta-analysis of 14 randomized controlled trials (RCTs), there is no evidence to support the routine use of antibiotic prophylaxis in patients with severe acute pancreatitis [32]. It is, however, thought that impacts of prophylactic antibiotics vary between subgroups, because a recent Cochrane meta-analysis suggested a reduction in pancreatic infection in the subgroup of patients who received imipenem [33]. The meta-analysis team for JPN Guidelines 2015 focused on the timing of prophylactic antibiotics and conducted a meta-analysis [34] using six RCTs in which antibiotics were administered within 72 h after onset of symptoms or 48 h after admission. As a result, the mortality rates were significantly different for those taking antibiotics (7.4%), and controls (14.4%) (odds ratio [OR] 0.48; 95% confidence interval [CI] 0.25–0.94). Also, early prophylactic antibiotics use was associated with reduced incidence of infected pancreatic necrosis (antibiotics 16.3%, controls 25.1%; OR 0.55; 95% CI 0.33–0.92). In conclusion, early use of prophylactic antibiotics for acute necrotizing pancreatitis is associated with reduced mortality and lower incidence of infected pancreatic necrosis.

As of peritoneal lavage (PL) for acute pancreatitis, the results of 12 RCTs and one meta-analysis did not show any evidence to support it, although severity assessment and PL procedures were inconsistent. The meta-analysis team conducted a new meta-analysis using four or five RCTs [35–39] in which a PL procedure was almost identical, concerning mortality and development of major complications. As a result, PL did not exert any effects on the survival rate, incidence of complications or length of hospital stay (Fig. 1),

<Mortality>

Study or subgroup	Experimental		Control			Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Cooper 1982	3	9	7	14	12.4%	0.50 [0.09, 2.84]
Inse 1986	4	19	1	20	2.6%	5.07 [0.51, 50.21]
Mayer 1985	12	45	13	46	32.0%	0.92 [0.37, 2.32]
Stone 1980	5	34	9	36	25.3%	0.52 [0.15, 1.74]
Zhang 2007	0	45	9	59	27.7%	0.06 [0.00, 1.03]
Total (95% CI)		152		175	100.0%	0.64 [0.36, 1.13]
Total events	24		39			

Heterogeneity, Chi^2=6.61, df=4 (P=0.16); I^2=39%
Test for overall effect: Z=1.53 (P=0.13)



<Major complications>

Study or subgroup	Experimental		Control			Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Cooper 1982	3	9	3	14	16.4%	1.83 [0.28, 12.07]
Ihse 1986	8	19	6	20	24.2%	1.70 [0.45, 6.36]
Mayer 1985	12	45	25	46	32.6%	0.31 [0.13, 0.74]
Stone 1980	5	34	13	36	26.9%	0.31 [0.09, 0.98]
Total (95% CI)		107		116	100.0%	0.64 [0.24, 1.61]
Total events	28		47			

Heterogeneity, Tau^2=0.53, Chi^2=7.0, df=3 (P=0.07); I^2=57%
Test for overall effect: Z=0.98 (P=0.33)

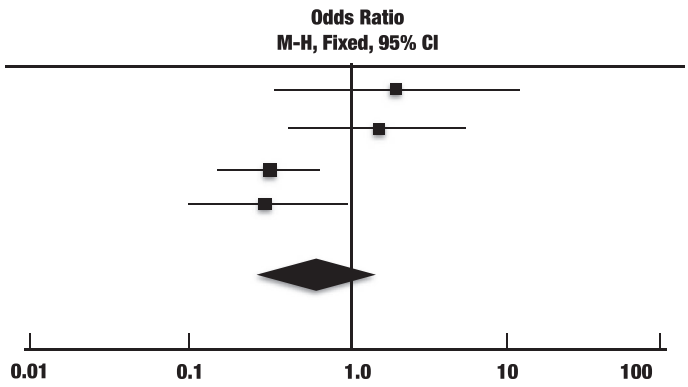


Fig. 1 Meta-analysis of randomized controlled trials (RCTs) for the effects of peritoneal lavage on mortality and the incidence of major complications (performed by the meta-analysis team of JPN Guidelines 2015).

concluding that PL is not recommended for the management of acute pancreatitis.

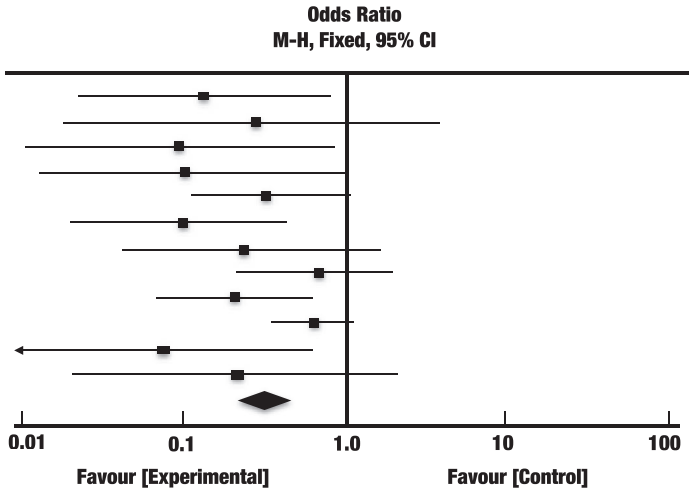
Acute pancreatitis remains the most common complication of endoscopic retrograde cholangiopancreatography (ERCP), being the reported incidence of 5–10% of cases and in 20–40% of certain high-risk procedures. Concerning the effect of prophylactic pancreatic stent placement for preventing post-ERCP pancreatitis, guidewire cannulation (cannulation of the bile duct and pancreatic duct by a guidewire inserted through a catheter) has been believed to decrease the risk of pancreatitis by avoiding hydrostatic injury to the pancreas that may occur with the use of radiocontrast agents. A number of RCTs and meta-analyses have been performed on prophylactic temporary pancreatic stent placement for high-risk groups of post-ERCP pancreatitis. In most studies, stent placement is reported to be effective for preventing pancreatitis, although the previous meta-analyses included the same cohort studies. The meta-analysis team conducted a new meta-analysis using 12 RCTs [40–51] in which inclusion criteria were strictly defined as the high-risk groups for post-ERCP pancreatitis (Fig. 2). The high-risk group for post-ERCP pancreatitis refers to patients with confirmed or suspected Sphincter of Oddi dysfunction, for whom cannulation is difficult, for whom pre-cut sphincterotomy has been performed, or for whom balloon dilatation has been provided. As a result, a significant reduction of post-ERCP pancreatitis including severe pancreatitis was observed in the group treated with the guidewire method.

Although a large number of pharmacologic drugs for preventing post-ERCP pancreatitis have been studied [52], their results have been disappointing. The most promising group of drugs to attenuate the inflammatory response of AP are non-steroidal anti-inflammatory drugs (NSAIDs) [53].

<Prevention of post-ERCP pancreatitis>

Study or subgroup	Experimental		Control			Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Fezel 2003	2	40	10	36	8.3%	0.14 [0.03, 0.68]
Harewood 2005	1	11	2	8	1.8%	0.30 [0.02, 4.06]
Ito 2010	1	35	8	35	6.5%	0.10 [0.01, 0.84]
Kawaguchi 2012	1	60	8	60	6.5%	0.11 [0.01, 0.91]
Lee 2012	6	50	15	51	10.9%	0.33 [0.12, 0.93]
Pan 2011	4	20	14	20	9.3%	0.11 [0.03, 0.46]
Patel 1999	2	18	6	18	4.4%	0.25 [0.04, 1.46]
Smithline 1993	6	48	9	50	6.4%	0.65 [0.21, 1.99]
Sofuni 2007	3	98	14	103	11.0%	0.20 [0.06, 0.72]
Sofuni 2011	20	213	31	213	23.4%	0.61 [0.33, 1.11]
Taransky 1998	1	41	10	39	8.3%	0.07 [0.01, 0.60]
Tsuchiya 2007	1	32	4	32	3.2%	0.23 [0.02, 2.14]
Total (95% CI)		666		665	100.0%	0.31 [0.21, 0.44]
Total events	48		131			

Heterogeneity, Chi^2=14.11, df=11 (P=0.23); I^2=22%
Test for overall effect: Z=6.53 (P<0.00001)



<Prevention of severe post-ERCP pancreatitis>

Study or subgroup	Experimental		Control			Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Fezel 2003	0	40	3	36	30.4%	0.12 [0.01, 2.37]
Ito 2010	0	35	0	35		Not estimable
Kawaguchi 2012	0	60	0	60		Not estimable
Lee 2012	0	50	1	51	12.3%	0.33 [0.01, 8.38]
Patel 1999	0	18	1	18	12.2%	0.32 [0.01, 8.27]
Smithline 1993	0	48	2	50	20.3%	0.20 [0.01, 4.28]
Sofuni 2007	0	98	0	103		Not estimable
Sofuni 2011	0	213	1	213	12.5%	0.33 [0.01, 8.19]
Taransky 1998	0	41	0	39		Not estimable
Tsuchiya 2007	0	32	1	32	12.3%	0.32 [0.01, 8.23]
Total (95% CI)		635		637	100.0%	0.24 [0.07, 0.85]
Total events	0		9			

Heterogeneity, Chi^2=0.37, df=5 (P=1.00); I^2=0%
Test for overall effect: Z=2.21 (P=0.03)

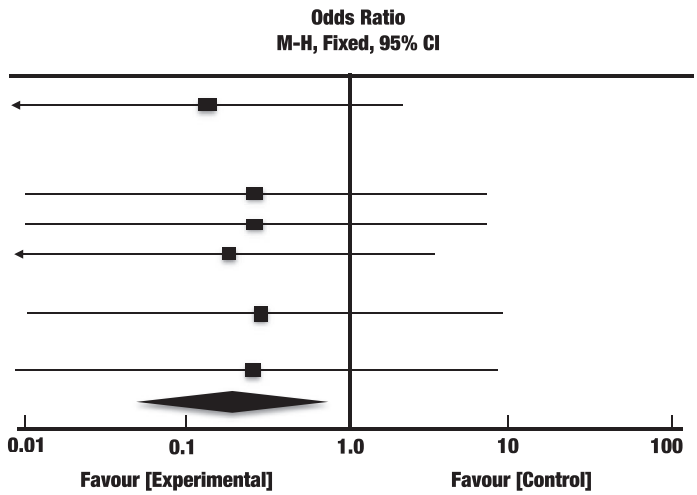


Fig. 2 Meta-analysis of randomized controlled trials (RCTs) for the effects of prophylactic pancreatic stent placement on the prevention of post-ERCP pancreatitis including severe cases (performed by the meta-analysis team of JPN Guidelines 2015).

The meta-analysis team performed a new meta-analysis using seven RCTs [54–60] on the effect of rectal NSAIDs in the prevention of post-ERCP pancreatitis including severe cases, which demonstrated that rectal NSAIDs could prevent post-ERCP pancreatitis but not development of severe post-ERCP pancreatitis (Fig. 3).

3) Flow chart

When we compared the flowcharts for the management of severe acute pancreatitis between the JPN Guidelines 2010 and 2015 as shown in Figures 4 and 5, the status of optional treatments such as intra-arterial infusion therapy, which is known as continuous regional arterial infusion (CRAI) of protease inhibitors and/or antibiotics [61], and blood purification therapy (CHDF), has become more optional in the JPN Guidelines 2015. Furthermore, the definition of local complications after acute pancreatitis and their approach have been extensively changed not only because the term of pancreatic abscess, which was defined as a localized collection of purulent material without significant necrotic material in the original Atlanta Classification [13], had been discarded in the revised Atlanta Classification, but also because the concept of step-up approach to the local complications has been adopted in the Guidelines 2015.

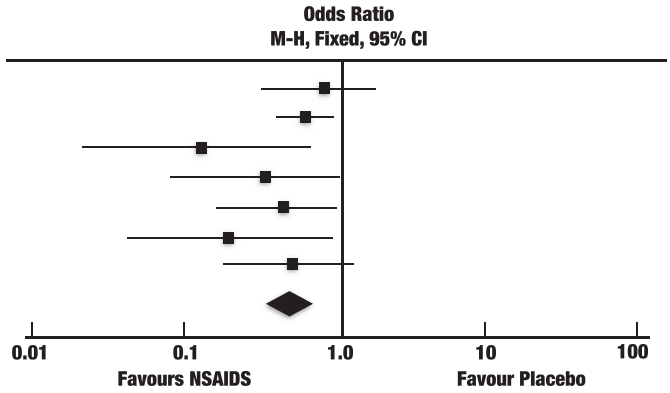
4) Recommendation

In comparison with the recommendations between JPN Guidelines 2010 and 2015, we could list distinct different points in Tables 2 and 3. According to the new meta-analysis on the effect of prophylactic antibiotics conducted by the meta-analysis team of the JPN Guidelines 2015, the recommendation sentence has been changed from "effective in reducing the frequency of complications related to infections" to "may improve the prognosis, if carried out in the early phases of pancreatitis (within 72 h of onset)". The timing of starting prophylactic antibiotics administration is clearly mentioned in the revised guidelines. As of intravenous administration of protease inhibitor, the revised guidelines do not support its use including continuous high-dose intravenous administration for severe cases. Enteral nutrition in the early phase is more strongly recommended in the revised guidelines, stating that it is desirable to be started within at least 48 h of admission. The role of continuous blood purification therapy such as CHF/CHDF has been changed from prevention of multiple organ failure to the indication for patients with

<Prevention of post-ERCP pancreatitis>

Study or subgroup	NSAIDs		Placebo			Odds Ratio
	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Dobronte 2013	11	130	11	98	9.4%	0.73 [0.30, 1.76]
Elmunzer 2012	27	295	52	307	38.1%	0.49 [0.30, 0.81]
Khoshbaten 2007	2	50	13	50	10.3%	0.12 [0.03, 0.56]
Montano 2007	4	75	12	75	9.3%	0.30 [0.09, 0.96]
Murray 2003	7	110	17	110	13.1%	0.37 [0.15, 0.94]
Otsuka 2012	2	51	10	53	7.8%	0.18 [0.04, 0.85]
Sotoudehmanesh 2007	7	245	15	245	12.0%	0.45 [0.18, 1.13]
Total (95% CI)		956		938	100.0%	0.41 [0.30, 0.57]
Total events	60		130			

Heterogeneity, Chi^2=6.14, df=6 (P=0.41); I^2=2%
Test for overall effect: Z=5.37 (P<0.00001)



<Prevention of severe post-ERCP pancreatitis>

Studies	Estimate (95% C.I)	Ev/Trt	Ev/Crt
Murray 2003	0.260 (0.027, 2.529)	0/110	2/110
Montano 2007	1.000 (0.020, 50.397)	0/75	0/75
Elmunzer 2012	1.041 (0.209, 5.194)	3/295	3/307
Otsuka 2012	1.038 (0.021, 52.372)	0/51	0/53
Overall (I^2=0%, p=0.794)	0.711 (0.217, 2.329)	3/531	5/545

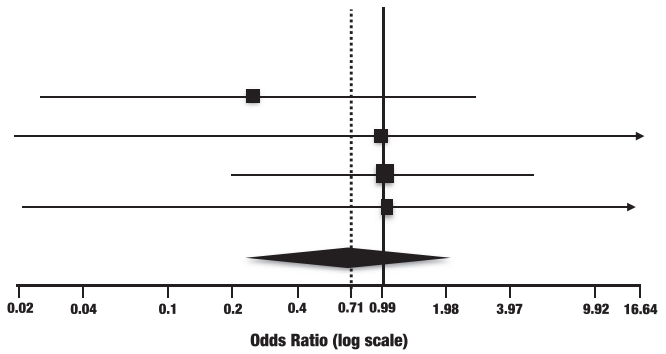


Fig. 3 Meta-analysis of randomized controlled trials (RCTs) for the effect of rectal non-steroidal anti-inflammatory drugs (NSAIDs) on the prevention of post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis including severe cases (performed by the meta-analysis team of JPN Guidelines 2015).

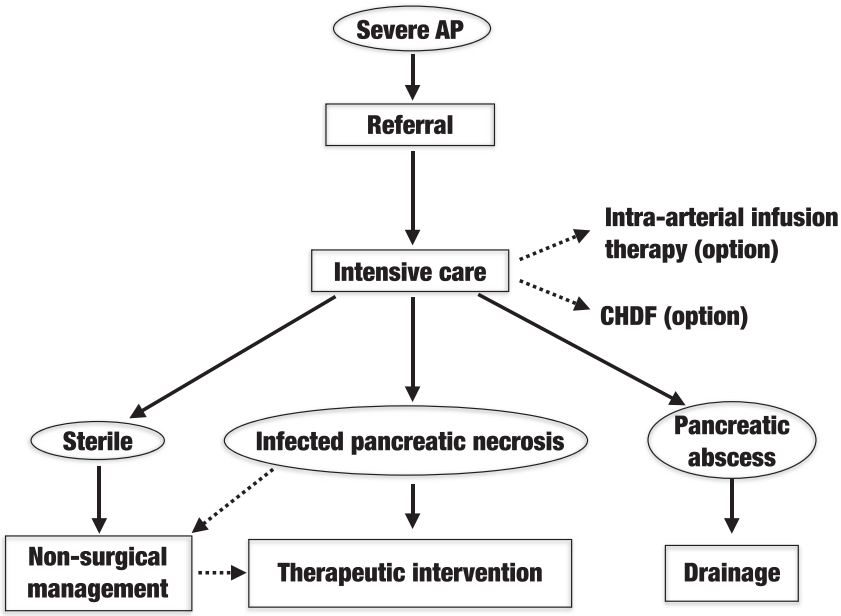


Fig. 4 Flowchart for the management of severe acute pancreatitis being adopted in JPN Guidelines 2010 (modified from reference 28).

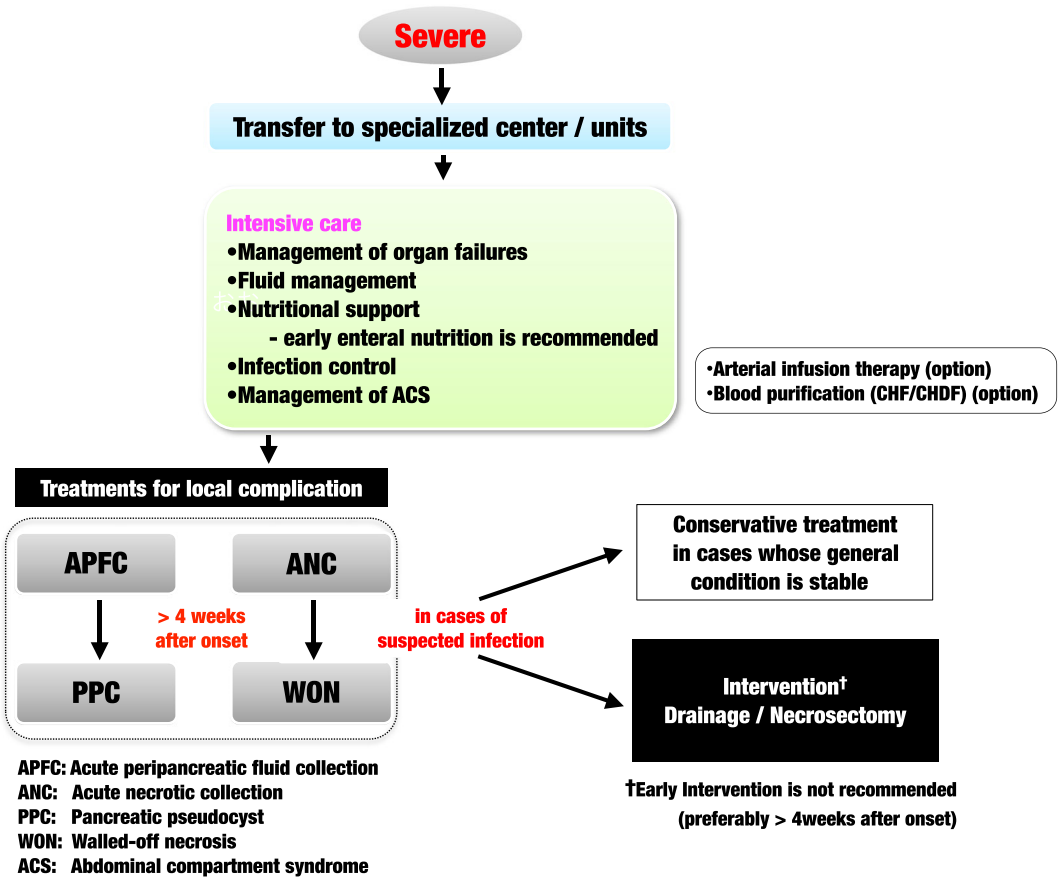


Fig. 5 Flowchart for the management of severe acute pancreatitis being adopted in JPN Guidelines 2015 (modified from reference 16).

anuria and/or abdominal compartment syndrome (ACS), being shifted from "non-renal indication" to "renal indication". CRAI, which was originally introduced to clinical use in Japan [61], has been changed from recommendation C1 to ungraded B, because one RCT, in which some bias could not be ruled out, demonstrated that this therapy significantly

Table 2 Comparison of recommendations between the JPN guidelines 2010 and 2015: prophylactic antibiotics, protease inhibitor, nutritional support, intensive care and abdominal compartment syndrome.

JPN 2010	JPN 2015
Prophylactic antibiotic	**Antibiotics prophylaxis**
Prophylactic administration of broad-spectrum antibiotics with good tissue penetration in severe acute pancreatitis is effective in reducing the frequency of complications related to infections. (Recommendation B)	The prophylactic administration of antibiotics in severe acute pancreatitis and necrotizing pancreatitis may improve the prognosis, if carried out in the early phases of pancreatitis (within 72 h of onset). (2B)
Protease inhibitor	**Protease inhibitor**
Continuous intravenous infusion of a large dose of protease inhibitors may reduce the mortality rate of severe acute pancreatitis and the frequency of complications in the early phase of severe acute pancreatitis. (Recommendation C1)	The effectiveness of intravenous administration of protease inhibitor (gabexate mesilate) for improving the life prognosis and the rate of complications of acute pancreatitis has not been clearly proven. Further consideration of the efficacy of continuous high-dose intravenous administration for severe cases is required. (ungraded B)
Nutritional support	**Nutritional support**
If there is no ileus, enteral nutrition initiated in the early phase of severe acute pancreatitis is superior to intravenous hyperalimentation. (Recommendation B)	If initiated in the early phase, enteral nutrition can reduce the incidence of complications and can contribute to an increased rate of survival. Therefore, it is desirable that it be started within at least 48 h of admission. (2A)
Intensive care	**Intensive care**
Continuous blood purification therapy performed in the early phase of severe acute pancreatitis is likely to prevent progression to multiple organ failure. (Recommendation C1)	For severe cases where circulation dynamics are not stable with anuria even after sufficient initial fluid infusion or cases with abdominal compartment syndrome (ACS), CHF/CHDF should be introduced. (1C)
Intra-arterial local infusion of protease inhibitors and antibiotics in the early phase of the disease may lead to a decrease in the mortality rate of acute necrotizing pancreatitis and in the frequency of infectious pancreatic complications. (Recommendation C1)	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)
Abdominal compartment syndrome not listed	**Abdominal compartment syndrome**
Blank	The sequential measurement of IAP is recommended for cases with excessive fluid infusion, high severity, renal and respiratory disorder complications, and fluid accumulation in multiple areas as observed by CT, since the onset of ACS increases the mortality rate in such cases. (2C)
Blank	When there is persistent or recurrent IAP $\geqq$ 12 mmHg, conservative treatment (gastrointestinal decompression, intra-abdominal decompression, improvement of abdominal wall compliance, appropriate fluid infusion and circulation management) should be initiated. The goal should be to manage for IAP $\leqq$ 15 mmHg. Surgical decompression should be considered only when internal treatment is not effective for patients with IAP $\geqq$ 20 mmHg and where the additional complication of organ failure is of concern. (2D)

reduced mortality rate compared to the control [62]. Recently, however, the effectiveness of CRAI was evaluated by comparison between the CRAI and non-CRAI groups, using propensity score analysis to adjust for treatment selection bias, which was based on data from a national administrative database covering 1,032 Japanese hospitals (a total of 17,415 eligible patients) [63]. As a result, CRAI was not effective in reducing in-hospital mortality rate, but was associated with longer hospital stay and higher costs. ACS, which was not mentioned at all in the previous version, has been adopted in the revised one, because it has been known in recent years that multiple organ failure in patients with severe acute pancreatitis is closely correlated with intra-abdominal hypertension and ACS [64].

Therapeutic intervention and surgery of acute pancreatitis in the Guidelines 2010 have been dramatically revised into intervention for the local complications in the Guidelines 2015, as shown in Table 3, by incorporating the revised Atlanta Classification and the confirmed evidence of step-up approach for necrotizing pancreatitis [65]. Especially, the role of fine-needle aspiration (FNA) has become less important to make a definitive diagnosis of infected pancreatic necrosis, not only because percutaneous drainage or endoscopic drainage is frequently performed if infected necrosis is suspected, but also because there is no evidence that the benefits of FNA, shortening the period to diagnosis and tailoring antibiotic treatment, improve the outcome. The results of new meta-analyses on post-ERCP pancreatitis performed by the

Table 3 Comparison of recommendations between the JPN guidelines 2010 and 2015: therapeutic intervention for the local complications, post-ERCP pancreatitis and pancreatic bundle.

JPN 2010	JPN 2015
Therapeutic intervention and surgery of acute pancreatitis	**Intervention for the local complications**
Conservative treatment should be performed as a rule in sterile pancreatic necrosis. (Recommendation B). Infected pancreatic necrosis is an indication for interventional therapy including surgery, interventional radiology (IVR) and endoscopic treatment. (Recommendation B). However, follow-up while giving conservative treatment by means of antibiotic administration is also available in patients who are in stable general condition. (Recommendation C)	In principle, conservative treatment should first be performed for necrotizing pancreatitis. The best indication for intervention is applied to cases of infected pancreatic necrosis with suspected or confirmed infection accompanying an aggravated general condition. (1C)
Bacteriological examination by means of fine needle aspiration is useful for making a definitive diagnosis of infected pancreatic necrosis. (Recommendation A)	Infected pancreatic necrosis should be suspected when clinical symptoms and blood test findings deteriorate. Routine use of FNA is not required for diagnosis, and clinical signs and CT should be used for a comprehensive determination. If an aggravated general condition is observed, percutaneous drainage or endoscopic drainage should be given for diagnosis and treatment. (1C)
Early surgery for necrotizing pancreatitis is not recommended. (Recommendation D). If surgery (necrosectomy) is performed, it should be delayed as long as possible. (Recommendation C1)	If possible, therapeutic intervention for infected pancreatic necrosis should be performed after 4 weeks of onset, when the necrosis has been sufficiently walled off, or in other words, during WON period. (2C)
Necrosectomy is recommended as a surgical procedure for infected necrosis. (Recommendation A)	During therapeutic intervention for infected pancreatic necrosis, percutaneous (retroperitoneal) drainage or endoscopic transluminal drainage should be first given, and if no improvement is achieved, necrosectomy should then be performed. Necrosectomy by endoscopic or retroperitoneal approach is recommended. (2B)
Drainage including percutaneous, endoscopic and surgical procedure should be performed for pancreatic abscess. (Recommendation B). If the clinical findings of pancreatic abscess are not improved by percutaneous or endoscopic drainage, surgical drainage should be performed immediately. (Recommendation B)	Blank
Interventional treatment should be performed for pancreatic pseudocysts that give rise to symptoms, accompany complications or increase the diameter of cysts. (Recommendation A). Percutaneous drainage, endoscopic drainage or surgical procedures are selected in accordance with the conditions of individual cases including the communication with the the positional relationship between the digestive tract walls. (Recommendation A)	Blank
Post-ERCP pancreatitis	**Post-ERCP pancreatitis**
Prophylactic pancreatic stent placement is useful in the high-risk group of post-ERCP pancreatitis. (Recommendation B). As for pharmacological prophylaxis, there is a possibility that nonsteroidal anti-inflammatory drugs (NSA-IDs) will be useful. (Recommendation C1)	Prophylactic temporary pancreatic stent placement is useful as an effective endoscopic procedure for the prevention of post-ERCP pancreatitis. This should only be performed in the high-risk groups for post-ERCP pancreatitis given the risks and cost. (2A). 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)
Efficacy of the bundle	**Pancreatitis bundle**
It is thought that when relevant and desirable care related to each other as a bundle has been delivered, the improvement in the prognosis of patients is more remarkable than when individual intervention has been delivered separately.	A high rate of implementation of the pancreatitis bundles may contribute to improving prognosis of patients with severe acute pancreatitis. (1C)

meta-analysis team for JPN Guidelines 2015 have upgraded the roles of prophylactic pancreatic stent placement and rectal NSAIDs from recommendation C1 in the former version to 2A in the revised version, respectively.

Pancreatitis bundles, which consist of 10 statements and specify the management and treatment within the first 48 h after the onset of severe acute pancreatitis, were established in the JPN Guidelines 2010 for the purpose of improving the mortality. Therefore, a nationwide survey of patients who developed acute pancreatitis in 2011 in Japan was conducted to explore the effect of following or not following the pancreatitis bundles on the mortality of a total of 505 severe acute pancreatitis patients. It was demonstrated that the implementation of statement No.6, which refers to initial

Table 4 Comparison of recommendations in most up-to-date guidelines with high quality scores: severity assessment, antibiotics phrophylaxis,protease inhibitor, nutritonal support, and intensive care

JPN 2015	IAP/APA 2013	ACG 2013
Severity assessment	**Prognostication/prediction of severity**	**Predicting severe AP**
It is recommended that a scoring system is used for severity assessments. (1B)	Systemic inflammatory response syndrome (SIRS) is advised to predict severe acute pancreatitis at admission and persistent SIRS at 48 h. (GRADE 2B, weak agreement)	In general, acute pancreaitits-specific scoring systems have a limited value, as they provide little additional information to the clinician in the evaluation of patients and may delay appropriate management.
Antibiotics prophylaxis	**Preventing infectious complications**	**The role of antibiotics in acute pancreatitis**
The prophylactic administration of antibiotics in severe acute pancreatitis and necrotizing pancreatitis may improve the prognosis, if carried out in the early phases of pancreatitis (within 72 h of onset). (2B)	Intravenous antibiotic prophylaxis is not recommended for the prevention of infectious complications in acute pancreatitis. (GRADE 1B, strong agreement)	Routine use of prophylactic antibiotics in patients with severe acute pancreatitis is not recommended (strong recommendation, moderate quality of evidence).
Protease inhibitor	**Protease inhibitor not listed**	**Protease inhibitor not listed**
The effectiveness of intravenous administration of protease inhibitor (gabexate mesilate) for improving the life prognosis and the rate of complications of acute pancreatitis has not been clearly proven. Further consideration of the efficacy of continuous high-dose intravenous administration for severe cases is required. (ungraded B)	Blank	Blank
Nutritional support	**Nutritional support**	**Nutrition**
If initiated in the early phase, enteral nutrition can reduce the incidence of complications and can contribute to an increased rate of survival. Therefore, it is desirable that it be started within at least 48 h of admission. (2A)	Enteral tube feeding should be the primary therapy in patients with predicted severe acute pancreatitis who require nutritional support. (GRADE 1B, strong agreement)	In severe AP, enteral nutrition is recommended to prevent infectious complications. Parenteral nutrition should be avoided, unless the enteral route is not available, not tolerated, or not meeting caloric requirements.
Intensive care	**Intensive care management**	**Initial management**
For patients in shock or with dehydration in the early phases of acute pancreatitis, short-time rapid fluid resuscitation (150-600 ml/h: depending on the presence of shock and the dehydration level) is recommended. For severe cases where circulation dynamics are not stable with anuria even after sufficient initial fluid infusion or cases with abdominal compartment syndrome (ACS), CHF/CHDF should be introduced. (1C)	Goal directed intravenous fluid therapy with 5-10 ml/kg/h should be used initially until resuscitation goals are reached. (GRADE 1B, weak agreement)	Aggressive hydration, defined as 250-500 ml/h of isotonic crystalloid solution should be provided to all patients, unless cardiovascular and/or renal comorbidites exist. Early aggressive intravenous hydration is most beneficial the first 12–24 h, and may have little benefit beyond (strong recommendation, moderate quality of evidence).
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)	Prophylactic continuous regional arterial infusion of antibiotics appears to be somewhat promising but further studies are warranted. (in the section of systemic antibiotic prophylaxis)	Blank

fluid therapy, was associated with a significant reduction in mortality. Moreover, the mortality was significantly lower in the patients whose treatment satisfied more than eight statements than in those whose treatment satisfied seven or fewer statements [66]. In the revised version, therefore, the statement has been changed: a high rate of implementation of the pancreatitis bundles may contribute to improving prognosis of patients with severe acute pancreatitis.

Comparison between JPN Guidelines 2015 and the other two guidelines

A recent systematic review for the 30 guidelines for acute pancreatitis [12] selected the four most up-to-date guidelines with high AGREE (Appraisal of Guidelines for Research and Evaluation) scores of more than 70 [67]. The four guidelines with high AGREE score included IAP 2002 [68], BSG (British

Table 5 Comparison of recommendations in most up-to-date guidelines with high quality scores: therapeutic intervention for the local complications, post-ERCP pancreatitis and pancreatic bundle.

JPN 2015	IAP/APA 2013	ACG 2013
Intervention for the local complications	**Indications for intervention in necrotizing pancreatitis**	**The role of surgery**
In principle, conservative treatment should first be performed for necrotizing pancreatitis. The best indication for intervention is applied to cases of infected pancreatic necrosis with suspected or confirmed infection accompanying an aggravated general condition. (1C)	Common indications for intervention in necrotizing pancreatitis are: 1) Clinical suspicion of, or documented infected necrotizing pancreatitis with clinical deterioration, preferably when the necrosis has become walled-off, 2) In the absence of documented infected necrotizing pancreatitis, ongoing organ failure for several weeks after the onset of acute pancreatitis, preferably when the necrosis has become walled-off. (GRADE 1C, strong agreement)	The presence of asymptomatic pseudocysts and pancreatic and/or extrapancreatic necrosis do not warrant intervention, regardless of size, location, and/or extension (strong recommendation, moderate quality of evidence).
Infected pancreatic necrosis should be suspected when clinical symptoms and blood test findings deteriorate. Routine use of FNA is not required for diagnosis, and clinical signs and CT should be used for a comprehensive determination. If an aggravated general condition is observed, percutaneous drainage or endoscopic drainage should be given for diagnosis and treatment. (1C)	Routine percutaneous fine needle aspiration of peripancreatic collections to detect bacteria is not indicated, because clinical signs and imaging signs are accurate predictors of infected necrosis in the majority of patients. Although the diagnosis of infection can be confirmed by fine needle aspiration (FNA), there is a risk of false-negative results. (GRADE 1C, strong agreement)	Increased use of conservative management and minimally invasive drainage have decreased the use of FNA for the diagnosis of infected necrosis. A consensus conference concluded that FNA should only be used in select situations where there is no clinical response to antibiotics, such as when a fungal infection is suspected (no recommendation).
If possible, therapeutic intervention for infected pancreatic necrosis should be performed after 4 weeks of onset, when the necrosis has been sufficiently walled off, or in other words, during WON period. (2C)	For patients with proven or suspected infected necrotizing pancreatitis, invasive intervention (i.e. percutaneous catheter drainage, endoscopic transluminal drainage/necrosectomy, minimally invasive or open necrosectomy) should be delayed where possible until at least 4 weeks after initial presentation to allow the collection to become 'walled-off'. (GRADE 1C, strong agreement)	In stable patients with infected necrosis, surgical, radiologic, and/or endoscopic drainage should be delayed preferably for more than 4 weeks to allow liquefication of the contents and the development of a fibrous wall around the necrosis (walled-off necrosis) (strong recommendation, low quality of evidence).
During therapeutic intervention for infected pancreatic necrosis, percutaneous (retroperitoneal) drainage or endoscopic transluminal drainage should be first given, and if no improvement is achieved, necrosectomy should then be performed. Necrosectomy by endoscopic or retroperitoneal approach is recommended. (2B)	The optimal interventional strategy for patients with suspected or confirmed infected necrotizing pancreatitis is initial image-guided percutaneous (retroperitoneal) catheter drainage or endoscopic transluminal drainage, followed, if necessary, by endoscopic or surgical necrosectomy. (GRADE 1A, strong agreement)	In symptomatic patients with infected necrosis, minimally invasive methods of necrosectomy are preferred to open necrosectomy (strong recommendation, low quality of evidence).
Post-ERCP pancreatitis	**Post-ERCP pancreatitis not listed**	**Preventing post-ERCP pancreatitis**
Prophylactic temporary pancreatic stent placement is useful as an effective endoscopic procedure for the prevention of post-ERCP pancreatitis. This should only be performed in the high-risk groups for post-ERCP pancreatitis given the risks and cost. (2A) 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)	Blank	Pancreatic duct stents and/or postprocedure rectal non-steroidal anti-inflammatory drug (NSAID) suppositories should be utilized to lower the risk of severe post-ERCP pancreatitis in high-risk patients (conditional recommendation, moderate quality of evidence).
Pancreatitis bundle	**Pancreatitis bundle not listed**	**Pancreatitis bundle not listed**
A high rate of implementation of the pancreatitis bundles may contribute to improving prognosis of patients with severe acute pancreatitis. (1C)	Blank	Blank

Society of Gastroenterology) 2005 [69], ACG 2006 [70] and JPN 2006, among which the JPN Guidelines 2006 showed the highest score of 86. Thus, we compared recommendations among the three most recent guidelines with high scores previously determined: JPN 2015, IAP/APA 2013 and ACG 2013, as shown in Tables 4 and 5, featuring distinct different points.

For severity assessment, JPN 2015 recommends a scoring system, especially using the JPN Severity Score (JSS) revised in 2008 [23], while the other two guidelines do not recommend it. As of antibiotics prophylaxis, its use in early phase (within 72 h of onset) is recommended in JPN 2015 (2B), whereas the other two guidelines do not recommend its routine use. The role of protease inhibitor, which is an original pharmacological drug produced in Japan, had been positively mentioned in the previous versions of JPN Guidelines; however, JPN 2015 does not support its effect. Enteral nutrition is highly recommended in the three guidelines, although JPN 2015 emphasizes its early introduction within at least 48 h of admission. For intensive care of severe acute pancreatitis, aggressive hydration with isotonic crystalloid solution is recommended in the three guidelines, and JPN 2015 alone mentions the role of continuous blood purification therapy as renal indication. The role of CRAI for the treatment of severe acute/necrotizing pancreatitis is weakly recommended without agreement of the revision committee members (ungraded B) in JPN 2015, and IAP/APA 2013 also stated that CRAI of antibiotics is somewhat promising.

As shown in Table 5, an approach and management of local complications in necrotizing pancreatitis including infected necrosis are almost similar in the three guidelines, although precise description of recommendations are somewhat different. The roles of pancreatic duct stents and postprocedure rectal NSAID suppositories are almost the same between JPN 2015 and ACG 2013, while IAP/APA 2013 does not adopt these topics. JPN 2015 alone emphasizes the implementation of the pancreatitis bundles that specify the management and treatment within the first 48 h after the onset of severe acute pancreatitis, while the other two guidelines do not define the pancreatitis bundles.

Conclusion

By exploring major revision points in the JPN Guidelines 2015 from the previous version and by examining distinct points in comparison with the recent high quality guidelines of IAP/APA Guidelines 2013 and ACG Guidelines 2013, the JPN Guidelines 2015 prove to be the highest quality in terms of systematic literature review conducting original analyses by the meta-analysis team, determining the grading of recommendations and providing pancreatitis bundles.

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QR code (for iPhone and Android) The codes to download the mobile application can be found at http://www.jshbps.jp/en/guideline/jpn-guideline2015.html

References

1. Yadav D, Lowenfels AB. Trends in the epidemiology of the first attack of acute pancreatitis: a systematic review. Pancreas. 2006;33:323–30.
2. Sekimoto M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: epidemiology, etiology, natural history, and outcome predictors in acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13:10–24.
3. Shimosegawa T. Summary of reports from 2011 to 2013 by The Intractable Pancreatic Disease Investigation and Research Group of the Japanese Ministry of Health, Labour and Welfare, 2014. p. 61–73. (in Japanese)
4. Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, Sekimoto M, et al. JPN Guidelines for the management of acute pancreatitis: cutting-edge information. J Hepatobiliary Pancreat Surg. 2006;13:2–6.
5. Yoshida M, Takada T, Kawarada Y, Hirata K, Mayumi T, Sekimoto M, et al. Health insurance system and payments provided to patients for the management of severe acute pancreatitis in Japan. J Hepatobiliary Pancreat Surg. 2006;13:7–9.
6. Koizumi M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13:25–32.
7. Hirota M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: severity assessment of acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13:33–41.
8. Takeda K, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: medical management of acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13:42–7.
9. Isaji S, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: surgical management. J Hepatobiliary Pancreat Surg. 2006;13:48–55.
10. Kimura Y, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN Guidelines for the management of acute pancreatitis: treatment of gallstone-induced acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13:56–60.
11. Mayumi T, Takada T, Kawarada Y, Hirata K, Yoshida M, Sekimoto M, et al. Management strategy for acute pancreatitis in the JPN Guidelines. J Hepatobiliary Pancreat Surg. 2006;13:61–7.
12. Loveday BP, Srinivasa S, Vather R, Mittal A, Petrov MS, Phillips AR, et al. High quantity and variable quality of guidelines for acute pancreatitis: a systematic review. Am J Gastroenterol. 2010;105:1466–76.
13. Bradley EL III. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute

Pancreatitis, Atlanta, GA, September 11 through 13, 1992. Arch Surg. 1993;128:586–90.
14. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Acute Pancreatitis Classification Working Group. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. Gut. 2013;62:102–11.
15. The Guideline Revision Committee for the management of acute pancreatitis 2015. Clinical Practice Guidelines for the Management of Acute Pancreatitist 2015, 4th edn. Tokyo: Kanehara & Co., Ltd.; 2015. (in Japanese)
16. Yokoe M, Takada T, Mayumi T, Yoshida M, Isaji S, Wada K, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. J Hepatobiliary Pancreat Sci. 2015; 22:405–32.
17. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. Pancreatology. 2013;13:e1–15.
18. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology. American College of Gastroenterology guideline: management of acute pancreatitis. Am J Gastroenterol. 2013; 108:1400–15.
19. Centre for Evidence-Based Medicine. Oxford Centre for Evidence-based Medicine - Levels of evidence (March 2009). Available from http://www.cebm.net/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/
20. Yoshida M, Takada T, Hirata K, Mayumi T, Shikata S, Shirai K, et al. Health insurance and payment systems for severe acute pancreatitis. J Hepatobiliary Pancreat Sci. 2010;17:13–6.
21. Sekimoto M, Shikata S, Takada T, Hirata K, Yoshida M, Hirota M, et al. Changes in management of acute pancreatitis before and after the publication of evidence-based practice guidelines in 2003. J Hepatobiliary Pancreat Sci. 2010;17:17–23.
22. Kiriyama S, Gabata T, Takada T, Hirata K, Yoshida M, Mayumi T, et al. New diagnostic criteria of acute pancreatitis. J Hepatobiliary Pancreat Sci. 2010;17:24–36.
23. Takeda K, Yokoe M, Takada T, Kataoka K, Yoshida M, Gabata T, et al. Assessment of severity of acute pancreatitis according to new prognostic factors and CT grading. J Hepatobiliary Pancreat Sci. 2010;17:37–44.
24. Hirota M, Takada T, Kitamura N, Ito T, Hirata K, Yoshida M, et al. Fundamental and intensive care of acute pancreatitis. J Hepatobiliary Pancreat Sci. 2010;17:45–52.
25. Amano H, Takada T, Isaji S, Takeyama Y, Hirata K, Yoshida M, et al. Therapeutic intervention and surgery of acute pancreatitis. J Hepatobiliary Pancreat Sci. 2010;17:53–9.
26. Kimura Y, Arata S, Takada T, Hirata K, Yoshida M, Mayumi T, et al. Gallstone-induced acute pancreatitis. J Hepatobiliary Pancreat Sci. 2010;17:60–9.
27. Arata S, Takada T, Hirata K, Yoshida M, Mayumi T, Hirota M, et al. Post-ERCP pancreatitis. J Hepatobiliary Pancreat Sci. 2010;17:70–8.
28. Wada K, Takada T, Hirata K, Mayumi T, Yoshida M, Yokoe M, et al. Treatment strategy for acute pancreatitis. J Hepatobiliary Pancreat Sci. 2010;17:79–86.
29. Mayumi T, Takada T, Hirata K, Yoshida M, Sekimoto M, Hirota M, et al. Pancreatitis bundles. J Hepatobiliary Pancreat Sci. 2010;17:87–9.
30. Takada T, Kawarada Y, Nimura Y, Yoshida M, Mayumi T, Sekimoto M, et al. Background: Tokyo Guidelines for the management of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Surg. 2007;14:1–10.
31. Andrews JC, Schünemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol. 2013;66:726–35.
32. Wittau M, Mayer B, Scheele J, Henne-Bruns D, Dellinger EP, Isenmann R. Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. Scand J Gastroenterol. 2011;46:261–70.
33. Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. Cochrane Database Syst Rev. 2010;5:CD002941.
34. Ukai T, Shikata S, Inoue M, Noguchi Y, Igarashi H, Isaji S, et al. Early prophylactic antibiotics administration for acute necrotizing pancreatitis: a meta-analysis of randomized controlled trials. J Hepatobiliary Pancreat Sci. 2015;22:316–21.
35. Cooper MJ, Williamson RC, Pollock AV. The role of peritoneal lavage in the prediction and treatment of severe acute pancreatitis. Ann R Coll Surg Engl. 1982;64:422–7.
36. Ihse I, Evander A, Gustafson I, Holmberg JT. Influence of peritoneal lavage on objective prognostic signs in acute pancreatitis. Ann Surg. 1986;204:122–7.
37. Mayer AD, McMahon MJ, Corfield AP, Cooper MJ, Williamson RC, Dickson AP, et al. Controlled clinical trial of peritoneal lavage for the treatment of severe acute pancreatitis. N Engl J Med. 1985;312:399–404.
38. Stone HH, Fabian TC. Peritoneal dialysis in the treatment of acute alcoholic pancreatitis. Surg Gynecol Obstet. 1980;150:878–82.
39. Zahng HB, Han Y, Wu KC, Ding J, Fan DM, Liu LL, et al. Efficacy of continuous peritoneal lavage for severe acute pancreatitis: a prospective randomized controlled study of 104 cases. Chin J Pancreatol. 2007;7:353–6.
40. Fazel A, Quadri A, Catalano MF, Meyerson SM, Geenen JE. Does a pancreatic duct stent prevent post-ERCP pancreatitis? A prospective randomized study. Gastrointest Endosc. 2003;57:291–4.
41. Harewood GC, Pochron NL, Gostout CJ. Prospective, randomized, controlled trial of prophylactic pancreatic stent placement for endoscopic snare excision of the duodenal ampulla. Gastrointest Endosc. 2005;62:367–70
42. Ito K, Fujita N, Noda Y, Kobayashi G, Obana T, Horaguchi J, et al. Can pancreatic duct stenting prevent post-ERCP pancreatitis in patients who undergo pancreatic duct guidewire placement for achieving selective biliary cannulation? A prospective randomized controlled trial. J Gastroenterol. 2010;45:1183–91.
43. Kawaguchi Y, Ogawa M, Omata F, Ito H, Shimosegawa T, Mine T. Randomized controlled trial of pancreatic stenting to prevent pancreatitis after endoscopic retrograde cholangiopancreatography. World J Gastroenterol. 2012;18:1635–41.
44. Lee TH, Moon JH, Choi HJ, Han SH, Cheon YK, Cho YD, Park SH, Kim SJ. Prophylactic temporary 3 F pancreatic duct stent to prevent post-ERCP pancreatitis in patients with a difficult biliary cannulation: a multicenter, prospective, randomized study. Gastrointest Endosc. 2012;76:578–85.
45. Pan XP, Dang T, Meng XM, Xue KC, Chang ZH, Zhang YP. Clinical study on the prevention of post-ERCP pancreatitis by pancreatic duct stenting. Cell Biochem Biophys. 2011;61:473–9.
46. Patel R, Tarnasky PR, Hennessy WS. Does stenting after pancreatic sphincterotomy reduce post-ERCP pancreatitis in patients with prior biliary sphincterotomy? Preliminary results of a prospective, randomized trial. Gastrointest Endosc. 1999; 49:80A.
47. Smithline A, Silverman W, Rogers D, Nisi R, Wiersema M, Jamidar P, et al. Effect of prophylactic main pancreatic duct stenting on the incidence of biliary endoscopic sphincterotomy-induced pancreatitis in high-risk patients. Gastrointest Endosc. 1993;39:652–57.
48. Sofuni A, Maguchi H, Itoi T, Katanuma A, Hisai H, Niido T, et al. Prophylaxis of post-endoscopic retrograde cholangiopancreatography pancreatitis by an endoscopic pancreatic spontaneous dislodgement stent. Clin Gastroenterol Hepatol. 2007;5:1339–46.
49. Sofuni A, Maguchi H, Mukai T, Kawakami H, Irisawa A, Kubota K, et al. Endoscopic pancreatic duct stents reduce the incidence of

post-endoscopic retrograde cholangiopancreatography pancreatitis in high-risk patients. Clin Gastroenterol Hepatol. 2011;9:851–8.
50. Tarnasky PR, Palesch YY, Cunningham JT, Mauldin PD, Cotton PB, Hawes RH. Pancreatic stenting prevents pancreatitis after biliary sphincterotomy in patients with sphincter of Oddi dysfunction. Gastroenterology. 1998;115:1518–24.
51. Tsuchiya T, Itoi T, Sofuni A, Itokawa F, Kurihara T, Ishii K, et al. Temporary pancreatic stent to prevent post endoscopic retrograde cholangiopancreatography pancreatitis: a preliminary, single-center, randomized controlled trial. J Hepatobiliary Pancreat Surg. 2007;14:302–7.
52. Badalov N, Tenner S, Baillie J. Prevention and treatment of post-ERCP pancreatitis. JOP. 2009;10:88–97.
53. Elmunzer BJ, Waljee AK, Elta GH, Taylor JR, Fehmi SM, Higgins PD. A meta-analysis of rectal NSAIDs in the prevention of post-ERCP pancreatitis. Gut. 2008;57:1262–7.
54. Döbrönte Z, Toldy E, Márk L, Sarang K, Lakner L. Effects of rectal indomethacin in the prevention of post-ERCP acute pancreatitis]. Orv Hetil. 2012;153:990–6.
55. Elmunzer BJ, Scheiman JM, Lehman GA, Chak A, Mosler P, Higgins PD, et al. U.S. Cooperative for Outcomes Research in Endoscopy (USCORE). A randomized trial of rectal indomethacin to prevent post-ERCP pancreatitis. N Engl J Med. 2012;366:1414–22.
56. Khoshbaten M, Khorram H, Madad L, Ehsani Ardakani MJ, Farzin H, Zali MR. Role of diclofenac in reducing post-endoscopic retrograde cholangiopancreatography pancreatitis. J Gastroenterol Hepatol. 2008;23:e11–16.
57. Montaño LA, Rodríguez LX, García CJE, Dávalos CC, Cervantes GG, Medrano MF, et al. Effect of the administration of rectal indomethacin on amylase serum levels after endoscopic retrograde cholangiopancreatography, and its impact on the development of secondary pancreatitis episodes. Rev Esp Enferm Dig. 2007;99:330–6.
58. Murray B, Carter R, Imrie C, Evans S, O'Suilleabhain C. Diclofenac reduces the incidence of acute pancreatitis after endoscopic retrograde cholangiopancreatography. Gastroenterology. 2003;124:1786–91.
59. Otsuka T, Kawazoe S, Nakashita S, Kamachi S, Oeda S, Sumida C, et al. Low-dose rectal diclofenac for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis: a randomized controlled trial. J Gastroenterol. 2012;47:912–7.
60. Sotoudehmanesh R, Khatibian M, Kolahdoozan S, Ainechi S, Malboosbaf R, Nouraie M. Indomethacin may reduce the incidence and severity of acute pancreatitis after ERCP. Am J Gastroenterol. 2007;102:978–83.
61. Takeda K, Matsuno S, Sunamura M, Kakugawa Y. Continuous regional arterial infusion of protease inhibitor and antibiotics in acute necrotizing pancreatitis. Am J Surg. 1996;171:394–8.
62. Piaścik M, Rydzewska G, Milewski J, Olszewski S, Furmanek M, Walecki J, et al. The results of severe acute pancreatitis treatment with continuous regional arterial infusion of protease inhibitor and antibiotic: a randomized controlled study. Pancreas. 2010;39:863–7.
63. Hamada T, Yasunaga H, Nakai Y, Isayama H, Horiguchi H, Matsuda S, Fushimi K, Koike K. Continuous regional arterial infusion for acute pancreatitis: a propensity score analysis using a nationwide administrative database. Crit Care. 2013;17:R214.
64. Al-Bahrani AZ, Abid GH, Holt A, McCloy RF, Benson J, Eddleston J, et al. Clinical relevance of intra-abdominal hypertension in patients with severe acute pancreatitis. Pancreas. 2008;36:39–43.
65. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. Dutch Pancreatitis Study Group. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010;362:1491–502.
66. Hirota M, Mayumi T, Shimosegawa T. Acute pancreatitis bundles: 10 clinical regulations for the early management of patients with severe acute pancreatitis in Japan. J Hepatobiliary Pancreat Sci. 2014;21:829–30.
67. AGREE Collaboration. Development and validation of an international appraisal instrument for assessing the quality of clinical practice guidelines: the AGREE project. Qual Saf Health Care. 2003;12:18–23.
68. Uhl W, Warshaw A, Imrie C, Bassi C, McKay CJ, Lankisch PG, et al. IAP Guidelines for the surgical management of acute pancreatitis. Pancreatology. 2002;2:565–73.
69. UK Working Party on Acute Pancreatitis. UK guidelines for the management of acute pancreatitis. Gut. 2005;54:iii1–9.
70. Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 2006;101:2379–400.