

REVIEW ARTICLE

Asian consensus statements on endoscopic management of walled-off necrosis Part 1: Epidemiology, diagnosis, and treatment

Hiroyuki Isayama,* Yousuke Nakai,* Rungsun Rerknimitr,[†] Christopher Khor,[‡] James Lau,[§] Hsiu-Po Wang,[¶] Dong Wan Seo,^{**} Thawee Ratanachu-ek,^{††} Sundeep Lakhtakia,^{‡‡} Tiing Leong Ang,^{§§} Shomei Ryozaawa,^{¶¶} Tsuyoshi Hayashi,^{***} Hiroshi Kawakami,^{†††} Natusyo Yamamoto,* Takuji Iwashita,^{‡‡‡} Fumihide Itokawa,^{§§§} Masaki Kuwatani,^{¶¶¶} Masayuki Kitano,^{****} Keiji Hanada,^{††††} Hirofumi Kogure,* Tsuyoshi Hamada,* Ryan Ponnudurai,^{‡‡‡‡} Jong Ho Moon,^{§§§§} Takao Itoi,^{§§§§} Ichiro Yasuda,^{¶¶¶¶} Atsushi Irisawa,^{*****} and Iruru Maetani,^{†††††}

*Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, †††††Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University Ohashi Medical Center and, §§§Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, ***Department of Gastroenterology, Hokkaido Cancer Center, †††Department of Gastroenterology and Hepatology and, ¶¶¶Division of Endoscopy, Hokkaido University Hospital, Sapporo, Department of Gastroenterology, ¶¶¶Saitama Medical University International Medical Center, Saitama, †††††Onomichi General Hospital, Onomichi, ¶¶¶¶Teikyo University Mizonokuchi Hospital, Kanagawa, *****Aizu Medical Center, Fukushima Medical University, Aizuwakamatsu, ††††First Department of Internal Medicine, Gifu University Hospital, Gifu, ****Department of Gastroenterology and Hepatology, Kinki University Faculty of Medicine, Osaka-sayama, Japan; †Division of Gastroenterology, Department of Medicine, Chulalongkorn University and, ††Department of Surgery, Rajavithi Hospital, Bangkok, Thailand; Department of Gastroenterology and Hepatology, †Singapore General Hospital and, §§Changi General Hospital, Singapore, Singapore; Department of Internal Medicine, §§§§Soon Chun Hyang University School of Medicine, Digestive Disease Center and Research Institute, Bucheon and **Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; §Department of Surgery, Endoscopic Center, Prince of Wales Hospital, The Chinese University of Hong Kong, Hong Kong, China; ¶Endoscopic Division, National Taiwan University Hospital, National Taiwan University, Taipei, Taiwan; ††Asian Institute of Gastroenterology, Hyderabad, India; and ††††Prince Court Medical Center, Kuala Lumpur, Malaysia

Key words

acute necrotizing pancreatitis, endoscopic necrosectomy, endoscopy, endosonography, walled-off necrosis.

Accepted for publication 22 March 2016.

Correspondence

Dr. Hiroyuki Isayama, Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo Bunkyo-ku, Tokyo 113-8655, Japan.
Email: isayama-ky@umin.ac.jp

Author contributions: HI was involved with study conception, study design, creation of the preliminary statements list and the allocated statement, drafting of the manuscript, critical revision of the manuscript, obtaining funding, face-to-face meetings, and voting. YN, NY, RR, and CK were involved with creation of the preliminary statements list and the allocated statement, drafting of the manuscript, critical revision of the manuscript, face-to-face meetings, and voting.

All authors were involved with creation of the allocated statement, drafting of the manuscript, critical revision of the manuscript, obtaining funding, face-to-face meetings, and voting.

Funding: An unrestricted education grant was provided by Century Medical Inc., FujiFilm Medical Corp., and Hitachi Medical Company.

Abstract

Walled-off necrosis (WON) is a relatively new term for encapsulated necrotic tissue after severe acute pancreatitis. Various terminologies such as pseudocyst, necroma, pancreatic abscess, and infected necrosis were previously used in the literature, resulting in confusion. The current and past terminologies must be reconciled to meaningfully interpret past data. Recently, endoscopic necrosectomy was introduced as a treatment option and is now preferred over surgical necrosectomy when the expertise is available. However, high-quality evidence is still lacking, and there is no standard management strategy for WON. The consensus meeting aimed to clarify the diagnostic criteria for WON and the role of endoscopic interventions in its management. In the Consensus Conference, 27 experts from eight Asian countries took an active role and examined key clinical aspects of WON diagnosis and endoscopic management. Statements were crafted based on literature review and expert opinion, employing the modified Delphi method. All statements were substantiated by the level of evidence and the strength of the recommendation. We created 27 consensus statements for WON diagnosis and management, including details of endoscopic procedures. When there was not enough solid evidence to support the statements, this was clearly acknowledged to facilitate future research. Proposed management strategies were formulated and are illustrated using flow charts. These recommendations, which are based on the best current scientific evidence and expert opinion, will be useful for guiding endoscopic management of WON. Part 1 of this statement focused on the epidemiology, diagnosis, and timing of intervention.

These sponsors did not participate in the literature search, consensus discussion, voting, lecture preparation, or manuscript preparation.

History of presentation: These consensus statements were presented at the Tokyo Conference of Asian Pancreato-biliary Interventional Endoscopy (T-CAP) 2014 in Tokyo, Japan and Asian Pacific Digestive Week (APDW) 2014 in Bali, Indonesia.

Introduction

Severe acute pancreatitis is a challenging disease for gastroenterologists. Severe acute pancreatitis with necrosis in the pancreatic parenchyma or surrounding fat tissue may lead to the formation of encapsulated fluid collections. Sometimes, this condition can be confused with pseudocyst or retention of pancreatic secretions due to disruption of the pancreatic duct. In the revised Atlanta classification of acute pancreatitis,¹ encapsulated necrotic tissues were defined as “walled-off necrosis (WON).” However, endoscopic management of WON has not yet been well established, and different conditions were described in previous publications. In addition, few studies have focused specifically on the management of WON.

Treatment strategies for infected WON can be challenging. While WON may be improved by drainage alone, most cases require necrosectomy because of the underlying infected solid necrotic tissue. Open surgical necrosectomy was the standard treatment for infected WON, but the procedure was associated with high morbidity and mortality. Endoscopic necrosectomy, which was first reported by Seifert *et al.* in 2000,² initially involves endoscopic transmural drainage (currently achieved mainly through endoscopic ultrasound [EUS] guidance, followed by direct insertion of the endoscope into the cavity for removal of necrotic tissue by irrigation, suction, and the use of endoscopic accessories). Since the first report by Seifert,² several larger series have been published with good outcomes. However, the exact role of endoscopic necrosectomy among other options in the management of WON remains to be clearly established.

Given the lack of high-level evidence regarding the endoscopic management of WON, a consensus group was convened to formulate recommendations for the management of WON. Specifically, these recommendations were formulated by combining a formal literature review of the diagnostic criteria and role of endoscopic management of WON with expert opinions from Asian endoscopists.

Methods

A modified Delphi process was employed to establish this consensus statement. The statement was established based on a literature review and a consensus among the panelists. A principal planning group created lists of statements that were distributed to all the members. Statements were made for clinical questions, and each clinical question was allocated to one or two of the members.

A comprehensive literature search was performed in the MEDLINE and EMBASE databases as well as the Cochrane Trials Register in human subjects. The key words used for searching were “Walled-off necrosis,” “Walled-off pancreatic necrosis,” “Severe acute pancreatitis,” “Necrotizing pancreatitis,” “Organized pancreatic necrosis,” “Pseudocyst,” “Endoscopic necrosectomy,” and “Necrosectomy.” The doctors allocated to each statement then carefully reviewed and selected the appropriate literature.

Faculty of the Tokyo Conference of Asian Pancreato-biliary Interventional Endoscopy (T-CAP; <http://www.t-cap.jp/>) formed the working group for this consensus statement. The members of this working group were from eight Asian countries: 17 from Japan; 2 each from Thailand, Singapore, and Korea; and 1 each from Taiwan, Hong Kong, Malaysia, and India. All T-CAP faculty members were pancreaticobiliary endoscopists, and all were gastroenterologists apart from two surgeons (TR and JL). The 17 Japanese members

were able to utilize the interventional radiology approach for treatment of WON when needed. Planning group members (HI, YN, NY, CK, and RR) created lists of statements and allocated them to the members. A face-to-face meeting was held in February 2014 in Tokyo. Each member made a presentation focusing on background, a summary of the scientific literature, the level of evidence, their proposed statement, and unanswered questions. Attendees discussed each statement, and amendments were made if needed. Thereafter, the statements were voted on by all attendees. Voting recommendations are shown in Table 1. The discussion was continued until an agreement of greater 80% for the A and B level of recommendations (accept completely and accept with some reservations) was reached. After the face-to-face meeting, each statement was corrected and presented again at the T-CAP annual meeting on June 27, 2014 in Tokyo and at Asian Pacific Digestive Week on October 24, 2014 in Bali for open discussion. Finally, the corrected statements were discussed among the faculty members via the Internet.

Consensus statements

1. Epidemiology

CQ1-1 What is the incidence of WON after acute pancreatitis?

Answer: The proportion of patients with necrotizing pancreatitis in a large series was 20–40%, and the proportion of WON cases treated with necrosectomy was 2–4%. We concluded that the incidence of WON should be between these figures.

Quality of evidence: III

Classification of recommendation: C

Level of agreement: a-100%, b-0%, c-0%, d-0%, e-0%

None of the studies analyzed cases with all types of WON (sterile or infected); rather, the studies analyzed cases of acute necrotizing pancreatitis (overestimation) or patients undergoing necrosectomy (underestimation). Because of the relatively recent introduction of the term “WON” in 2005, some studies referred to “infected necrotizing pancreatitis” or “infected pancreatic necrosis” and thus might include cases that were not WON. Previously, WON has also been described as “organized pancreatic necrosis,” “necroma,” “pancreatic sequestration,” “pseudocyst associated with necrosis,” and “subacute pancreatic necrosis.”

Patients with necrotizing pancreatitis develop necrosis of the pancreatic parenchyma, the peripancreatic tissue, or both, and some of these patients subsequently develop WON. To date, the incidence of WON has remained unknown because we only have data regarding the incidence of necrotizing pancreatitis and treated WON. Table 2 presents a literature review, and the incidence of necrotizing pancreatitis in large series studies was reported to be 22.9% (359 of 1568 cases),³ 29.7% (203 of 683),⁴ and 39.5% (121 of 306).⁵ The largest study, which included 9421 patients from China, reported that necrosectomy was performed in 412 patients (4.4%).⁶ Based on our review of the literature, the incidence of necrotizing pancreatitis in a large series was 20–40%; however, this figure overestimates the incidence of WON because patients with necrotizing pancreatitis do not necessarily develop WON. The incidence of WON in patients treated with necrosectomy was 2–4%, which is likely an underestimation of the overall incidence of WON. Therefore, we concluded that the overall incidence

Table 1 Quality of evidence, classification of recommendations, and voting schema of the modified Canadian Task Force on the Periodic Health Examination

Category and grade	Description
Quality of evidence	
I	Evidence obtained from at least 1 RCT.
II-1	Evidence obtained from well-designed control trials without randomization.
II-2	Evidence obtained from a well-designed cohort or case-control study.
II-3	Evidence obtained from comparisons between times and places with or without intervention.
III	Opinion of respected authorities based on clinical experience and expert committees
Classification of the recommendation	
A	There is good evidence to support the statement.
B	There is fair evidence to support the statement.
C	There is poor evidence to support the statement, but the recommendation was made on other grounds.
D	There is fair evidence to refute the statement.
E	There is good evidence to refute the statement.
Voting on the recommendation	
A	Accept completely
B	Accept with some reservations
C	Accept with major reservations
D	Reject with reservations
E	Reject completely

Table 2 Incidence of walled-off necrosis (WON)

Author	Year	Country	No. of patients	WON; number (%)
Hartwig ⁵	2002	Germany	306	121 (39.5)
Beger ³	2003	Germany	1568	359 (22.9)
Lee ⁷⁰	2006	Singapore	373	14 (3.8)
Mofidi ⁷¹	2007	UK	1248	233 (18.9)
Babu ²⁰	2010	UK	1535	28 (1.8)
Garg ⁴	2010	India	683	203 (29.7)
De Rai ⁷²	2010	Italy	1173	29 (2.5)
Beenen ²⁴	2011	New Zealand	577	25 (4.3)
Guo ⁶	2013	China	9421	412 (4.4)

of WON should be between these figures. All the attending physicians agreed that the literature was too limited to estimate the true incidence of WON and concluded that prospective data collection from a large number of outpatients/inpatients is required to clarify the true incidence of WON and the cause of WON.

Unanswered question: Due to the absence of an article evaluating the incidence of all types of WON, the incidence of WON is currently unknown.

CQ1-2 Are there any etiological factors that predispose a patient to develop WON?

Answer: While the most common causes of acute pancreatitis resulting in necrotizing pancreatitis or WON are biliary factors and alcohol consumption, no etiological factors have been identified that predispose a patient to develop necrotizing pancreatitis or WON.

Quality of evidence: III

Classification of recommendation: C

Level of agreement: a-90%, b-10%, c-0%, d-0%, e-0%

A considerably wide range of etiologies have been reported for acute pancreatitis, which can potentially cause WON. However, the distribution of the etiologies for WON has not been clarified. The largest study, which included 639 patients from the Netherlands, reported that the predominant cause of necrotizing pancreatitis was biliary factors (48%), followed by alcohol consumption (24%), and unknown factors (19%).⁷ Based on our review of the literature, the leading causes of acute pancreatitis resulting in WON were biliary factors (median 40%, range 14–81%), alcohol consumption (median 27%, range 2–70%), and idiopathic factors (median 14%, range 4–45%).^{6–38,41} In addition to these etiologies, underlying obesity can affect the clinical course of acute pancreatitis. Obesity, especially visceral fat,^{39,40} is a known risk factor for severe acute pancreatitis and was reported to cause more local complications including necrosis. Therefore, it is likely that obesity can be a risk factor for WON, although there were no high level clinical evidences.”

We reviewed the literature to estimate the proportions of etiologies leading to the development of WON; however, we acknowledge several biases. First, because most studies did not analyze all consecutive cases of WON, and only patients with WON who were undergoing necrosectomy were evaluated, the true underlying etiologies of all WON cases were unclear. Second, the lack of uniformity in terminology, as described in CQ 1-1, prevented an optimal estimation. Collection of prospective registry data from multiple centers based on the uniform definition of WON is necessary.

Unanswered question: The incidence of acute pancreatitis leading to WON with a rare etiology (e.g. pancreas divisum or drug-induced pancreatitis) is unknown. The natural courses and outcomes of WON have not been fully evaluated according to each etiology.

2. Diagnosis of WON

CQ.2. How can we make a diagnosis of WON?

Answer: WON is defined as a mature, encapsulated collection of necrotic pancreatic and/or peripancreatic tissue that develops ≥ 4 weeks after the onset of acute pancreatitis. Contrast-enhanced computed tomography (CE-CT) is commonly used as a standard technique to diagnose WON. Magnetic resonance imaging (MRI), transabdominal ultrasound (US), or EUS may be used as a complementary modality to better define the presence of a solid component.

Quality of evidence: II-3

Classification of recommendation: C

Level of agreement: a-95%, b-5%, c-0%, d-0%, e-0%

Walled-off necrosis is a relatively new clinical entity. The differential diagnosis of WON from pseudocyst is important because the treatment procedure for each disease is different, and these two entities are sometimes misdiagnosed.

To make the correct diagnosis, both imaging findings and clinical course are important. There are two types of acute pancreatitis defined in the Revised Atlanta Classification (2012): interstitial edematous pancreatitis and necrotizing pancreatitis. Four weeks after the onset of acute pancreatitis, acute peripancreatic fluid that collects and becomes encapsulated with a well-defined inflammatory wall is referred to as a “pseudocyst.” Pseudocysts contain mostly liquid components. On the other hand, necrotizing pancreatitis with acute necrotic collection develops into WON at 4 weeks after onset. WON is also a well-defined, encapsulated inflammatory collection similar to a pseudocyst, but solid components are present. The detection of solid components is important for distinguishing WON from pseudocyst using imaging modalities.

Contrast-enhanced computed tomography depicts “WON” as heterogeneous with liquid and non-liquid density with varying degrees of loculations (some may appear homogeneous).^{1,41} However, CE-CT may not readily distinguish solid content from liquid content in some cases (Fig. 1). MRI,^{1,42,43} transabdominal US^{1,42}, or EUS^{1,42} may be required for this distinction. MRI and US are also recommended especially for pregnant patients and for patients with renal insufficiency or allergy to iodine.^{42,44} US-guided or EUS-guided fine needle aspiration (FNA) might be available for a diagnosis of infected WON.^{1,42,45} We reviewed the reported literature in Table 3.

Unanswered question: What are the diagnostic yields of MRI and EUS for the detection of WON with solid components in fluid collections?

3. Diagnosis of infection

CQ3-1. What are the symptoms and imaging findings of infected WON?

Answer: Persistent sepsis or progressive clinical deterioration is indicative of infected WON. The presence of gas bubbles within the WON on computed tomography (CT) is suggestive of infection.

Quality of evidence: III

Classification of recommendation: C

Level of agreement: a-94%, b-6%, c-0%, d-0%, e-0%

A definitive diagnosis of infected WON is mandatory because the treatment strategy obviously differs from that utilized for sterile WON. However, optimal diagnostic methods that make use of imaging modalities and clinical findings have not yet been established. Therefore, signs of infection should be monitored carefully based on assessments of clinical manifestations as well as performance of blood tests, blood cultures, and CT scans, especially in the late phase of acute pancreatitis.

There have been no studies examining the diagnostic accuracy of imaging findings of infected WON. High-quality guidelines, which were evaluated by Loveday *et al.*,⁴⁶ described that “the presence of gas bubbles within pancreatic/peripancreatic necrosis” on CT was as an important indication of infection.^{47–49} Gas within the fluid collection sometimes suggests an underlying fistula to the gastrointestinal lumen, and the risk of infection can be higher in patients with fistula to the colon than to the duodenum. Therefore, when gas is seen within the fluid collection on the cross-sectional images, the presence of fistula and subsequent infection should be carefully evaluated. In addition to gas within the fluid collection, shrinkage of the cavity, bleeding within the cavity, and abdominal pain can be the signs of fistula formation to the gastrointestinal lumen. There were no significant differences in common clinical signs (e.g. elevated white blood cell counts or fever) between sterile and infected pancreatic/peripancreatic necrosis.⁵⁰ The relationship between the occurrence of infected pancreatic/peripancreatic necrosis and the severity of pancreatitis (extent of necrosis, occurrence of organ failure, and pulmonary, renal, and cardiocirculatory insufficiency) was well investigated; however, groups at high risk for developing infected WON were not clearly identified.^{51,52} Although definitive criteria do not exist, high-quality guidelines developed in the past decade stated that deterioration of the clinical course (e.g. systemic toxicity, organ

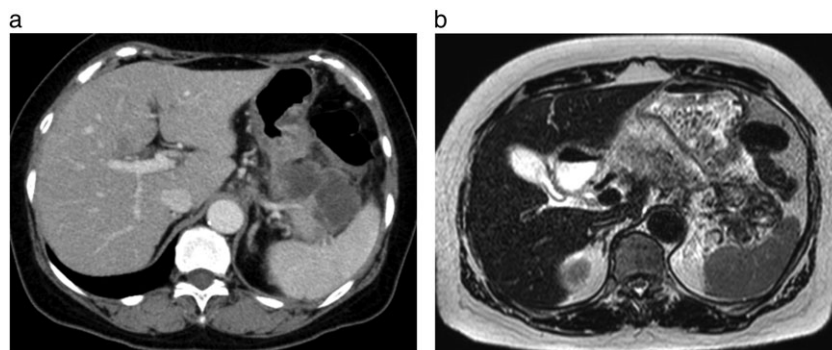


Figure 1 Detection of solid components in a cavity of walled-off necrosis (WON). (1a) Contrast-enhanced computed tomography did not reveal solid components in WON cavities. (1b) Magnetic resonance imaging showed solid components in WON cavities.

Table 3 Clinical studies examining the diagnosis of pancreatic necrosis or WON

Author	Year	No. of patients	Disease	Modality	Timing of imaging	Design	Pro/retro	Result
Mainwaring ⁷³	1989	40 (PNec 18)	PFC	CECT	During the 2 weeks preceding surgery	Observational/cross-sectional	Retrospective	CT grading (C, D, R): differentiation of Pct and PNec
Morgan ⁴³	1997	19 (18 patients)	PFC	MR/CECT/US	3–20 weeks (average 8 weeks)	Interventional/sequential comparison	Prospective	Solid debris: MR (89) = US > CT (22%) PNec: MR = CECT
Lecesne ⁷⁴	1999	30 (PNec?)	AP	MR/CECT	23 patients ≤ 1 week, 2 patients between 1 and 2 weeks, 5 patients ≥ 2 weeks	Observational comparison	Retrospective	
Hirota ⁷⁵	2002	21 (PNec 8)	PNec	MR/CECT	Acute phase	Observational/comparison	Prospective	MRI can discriminate (1) necrotic area, (2) perinecrotic fluid collection, (3) hemorrhagic foci
Arvanitakis ⁷⁶	2004	39 (PNec 6)	AP	MR/CECT	Days ≤ 3, 7, 30	Interventional/sequential comparison	Prospective	Staging AP severity: MR = CECT
Viremouneix ⁷⁷	2007	90 (PNec 12–19)	AP	MR/CECT	≤ 6 days	Interventional/sequential comparison	Prospective	Staging AP severity: MR > CECT
Takahashi ⁴¹	2008	78 (WOPN 45, Pct 28, Abscess 5)	PFC	CECT	During the week prior to endoscopic treatment	Observational/cross-sectional		CT can differentiate WOPN from Pct (79.5–83.6%)
Ocampo ⁷⁸	2009	129	PNec	CECT	Average 8.3 days	Observational/cross-sectional	Retrospective	Patients with peri-PNec: higher rates of infected PNec and mortality
Jurgensen ³⁰	2012	31	PNec	EUS	ND	Observational/cross-sectional	Retrospective	PNec with high liquid content: A high risk of complications

PFC, pancreatic fluid collection; Pct, pseudocyst; PNec, pancreatic necrosis; AP, acute pancreatitis; WON, walled-off necrosis; WOPN, walled-off pancreatic necrosis; CECT, contrast-enhanced computed tomography; MR, magnetic resonance; EUS, endoscopic ultrasound; US, transabdominal ultrasound; CT, computed tomography.

failure, or sepsis) indicates the occurrence of infected pancreatic/peripancreatic necrosis, especially in the late phase of acute pancreatitis (3 or more weeks after the onset of acute pancreatitis).^{47–49}

Unanswered question: What is the diagnostic accuracy of imaging findings of infected WON?

CQ3-2. Is image-guided FNA necessary for the diagnosis of infection?

Answer: Image-guided FNA is accurate tool for distinguishing sterile from infected WON. However, it is not always needed to establish a diagnosis of infection.

Quality of evidence: III

Classification of recommendation: C

Level of agreement: a-94%, b-6%, c-0%, d-0%, e-0%

A definitive diagnosis of infected WON can be made by positive culture of fluid in the WON cavity, which can be readily obtained by image-guided FNA (CT, US, or EUS). However, the indication for FNA and its impact on the management of WON have not been well established.

Several clinical studies have shown the safety and diagnostic validity of Gram's stain and culture of specimens obtained by percutaneous FNA from the necrotic area.^{8,50,52–56} High-quality guidelines in the past decade recommended that patients with suspected infected necrosis should undergo FNA to prove infection prior to (surgical) necrosectomy.^{47–49} The false-negative rate was reported to be 0–17% (median, 4%), even in studies in which repeat FNA was performed.^{50,52–55} Recent randomized controlled trials (RCTs) determined that patients without positive Gram's stain or culture were eligible for minimally invasive step-up intervention (i.e. percutaneous catheter drainage or endoscopic transluminal drainage) depending either on the deterioration of the clinical course (e.g. systemic toxicity, organ failure, or sepsis) or on the presence of gas bubbles within pancreatic/peripancreatic necrosis on CT.^{27,57}

The attendees disagreed that image-guided FNA (e.g. US-guided, EUS-guided, and CT-guided FNA) is indispensable for the diagnosis of infection. This procedure appears to be omitted in many hospitals because sonographers, radiologists, and endosonographers may not be routinely available. In addition, conservative treatments such as antimicrobial agents or minimally invasive interventions have been accepted as initial treatments, even in cases of suspected infected WON. Thus, the need for image-guided FNA seems to be limited in patients for whom highly invasive intervention is scheduled only if the presence of a bacterial infection is proven.

Unanswered question: Is FNA truly an indispensable modality for infected WON? When should we perform FNA for the diagnosis of WON?

4. Indication for treatment

CQ4-1. Is there a role for medical treatment of WON?

Answer: Yes. Medical treatment is the first step in the management of patients with WON.

Quality of evidence: II-2

Classification of recommendation: B

Level of agreement: a-100%, b-0%, c-0%, d-0%, e-0%

Medical treatment is the first step in the management of patients with WON. Patients will require supportive therapy, which includes systemic antibiotics, nutritional support, and other organ support such as mechanical ventilation and inotropic support as required.

Nutrition: A meta-analysis of RCTs has shown that in severe acute pancreatitis, including acute pancreatitis associated with WON, enteral nutrition decreased systemic infections, multi-organ failure, the need for surgical intervention, and mortality compared with parenteral nutrition.⁵⁸ Parenteral nutrition should be avoided unless enteral nutrition is not available, not tolerated, or not meeting the caloric needs of the patient.

Antibiotics: A meta-analysis of RCTs has shown that antibiotics do not prevent secondary infection of necrosis.⁵⁹ Hence, their role is only in the treatment of an active or suspected infection. Some reports have indicated that antibiotics alone may suffice for the treatment of infected WON in patients in good clinical condition. Thus, based on data from large case series, it is acknowledged that selected clinically stable patients with infected necrosis who are minimally symptomatic can be treated with antibiotics alone but require intervention if clinical deterioration occurs.^{56–59}

Drugs that suppress the secretion of pancreatic juice: Octreotide and somatostatin analogues are not recommended because they did not show significant effectiveness in the treatment of severe acute pancreatitis.⁶⁰

Protease inhibitors: Protease inhibitors lack a definite clinical benefit based on meta-analyses.^{61,62} The routine use of protease inhibitors is not recommended by current guidelines, and a recent review of a Japanese administrative dataset also did not show any benefits.⁶³

Antacid drugs: Histamine H2-receptor antagonist also failed to show any benefits for patients with acute pancreatitis. This was acknowledged in the 2006 Japanese guidelines.⁶⁴ A pilot RCT from Korea also showed no benefits of proton pump inhibitor therapy.⁶⁵

Unanswered question: Which medical treatments are effective during the necrosectomy procedure?

CQ4-2. What are the indications for drainage in WON?

Answer: Drainage (with or without necrosectomy) is recommended for symptomatic WON.

Quality of evidence: II-2

Classification of recommendation: C

Level of agreement: a-80%, b-15%, c-5%, d-0%, e-0%

A drainage procedure (with or without necrosectomy) is indicated for patients with symptomatic WON who are unresponsive to medical treatment. The modalities include an endoscopic approach, a percutaneous approach, and surgical necrosectomy. A recent RCT demonstrated that a minimally invasive step-up approach reduces mortality and major

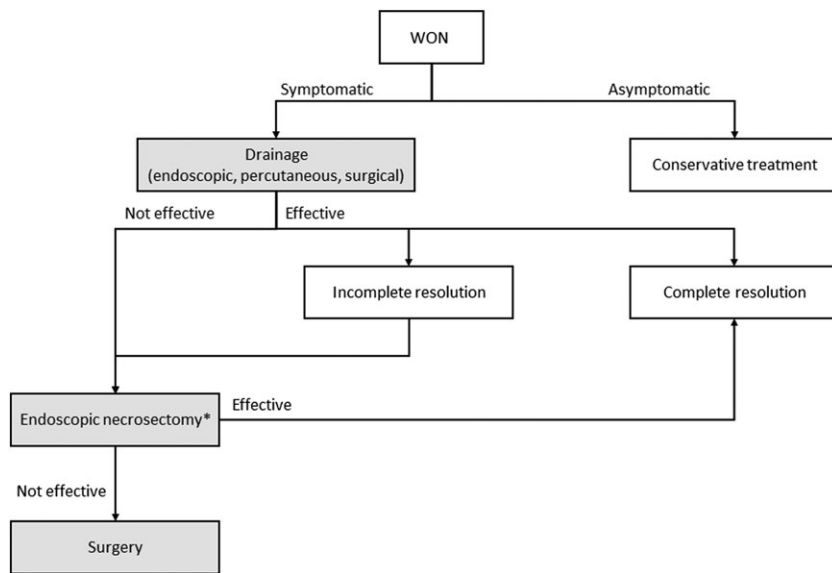


Figure 2 Flow chart illustrating the proposed management of walled-off necrosis (WON). *If endoscopic procedure is impossible, surgical or percutaneous necrosectomy will be performed.

complications from 69% to 40% compared with primary open necrosectomy.²²

Unanswered question: For patients with WON, when should we proceed directly to drainage without waiting for medical treatment failure?

5. Timing of necrosectomy

CQ5. Should we perform necrosectomy immediately after the diagnosis of WON?

Answer: The initial step for the treatment of symptomatic WON is either percutaneous or endoscopic drainage. Necrosectomy should then be considered if the drainage procedure is not effective.

Quality of evidence: II-2

Classification of recommendation: B

Level of agreement: a-68%, b-32%, c-0%, d-0%, e-0%

There are no clear criteria regarding when to proceed to necrosectomy. There are two types of treatment strategies for necrosectomy: necrosectomy during the initial drainage session (direct necrosectomy) and necrosectomy after a failed response to drainage (step-up approach). Based on the literature review, 35–55% of patients with infected WON can be treated successfully with percutaneous or endoscopic drainage alone.^{21,66,67} Mouli *et al.* pooled eight retrospective observational studies ($n=324$) on conservative treatment for patients with infected pancreatic necrosis and found that only 26% of them needed subsequent necrosectomy. In four observational studies ($n=157$) on drainage alone for infected pancreatic necrosis, 38% of patients underwent necrosectomy.⁶⁸ Although endoscopic necrosectomy is effective and requires a relatively short treatment period, it can cause serious complications including death. The morbidity and mortality rates in previous large-scale studies were reported to be 14–33% and 5.8–11%.^{17,26,36} Therefore, endoscopic necrosectomy should be considered only after the failure of the step-up approach.^{7,22,69}

Figure 2 presents a flowchart illustrating the WON management strategy proposed by this working group. Endoscopic management for infected WON should be considered if the patient fails to improve after the initial medical treatment and drainage. Surgical procedures should be considered when endoscopic necrosectomy is ineffective (See CQ 6 in Part 2).

Unanswered question: How can we predict which patients will require necrosectomy?

Summary

In summary, WON is a new term, and various terminologies were previously used in the literature, resulting in confusion. In addition, high-level evidence is still lacking regarding the endoscopic management of WON. We tried to make the consensus statements through a formal literature review in combination with expert opinions from Asian endoscopists. Part 1 of the Asian consensus statements regarding endoscopic management of WON in severe acute pancreatitis focused on the epidemiology, diagnosis, and timing of intervention. Part 2 of the Asian consensus statements highlight endoscopic management of WON and its adjunctive treatment.

References

- 1 Banks PA, Bollen TL, Dervenis C *et al.* Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102–11.
- 2 Seifert H, Wehrmann T, Schmitt T, Zeuzem S, Caspary WF. Retroperitoneal endoscopic debridement for infected peripancreatic necrosis. *Lancet* 2000; **356**: 653–5.
- 3 Beger HG, Rau B, Isenmann R. Natural history of necrotizing pancreatitis. *Pancreatology* 2003; **3**: 93–101.
- 4 Garg PK, Sharma M, Madan K, Sahni P, Banerjee D, Goyal R. Primary conservative treatment results in mortality comparable to surgery in patients with infected pancreatic necrosis. *Clin. Gastroenterol. Hepatol.* 2010; **8**: 1089–94 e2.

- 5 Hartwig W, Werner J, Muller CA, Uhl W, Buchler MW. Surgical management of severe pancreatitis including sterile necrosis. *J. Hepatobiliary Pancreat. Surg.* 2002; **9**: 429–35.
- 6 Guo Q, Lu H, Hu W, Zhang Z. A retroperitoneal approach for infected pancreatic necrosis. *Scand. J. Gastroenterol.* 2013; **48**: 225–30.
- 7 van Santvoort HC, Bakker OJ, Bollen TL *et al.* A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology* 2011; **141**: 1254–63.
- 8 Rodriguez JR, Razo AO, Targarona J *et al.* Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. *Ann. Surg.* 2008; **247**: 294–9.
- 9 Tzovaras G, Parks RW, Diamond T, Rowlands BJ. Early and long-term results of surgery for severe necrotising pancreatitis. *Dig. Surg.* 2004; **21**: 41–6; discussion 6–7.
- 10 Wig JD, Mettu SR, Jindal R, Gupta R, Yadav TD. Closed lesser sac lavage in the management of pancreatic necrosis. *J. Gastroenterol. Hepatol.* 2004; **19**: 1010–5.
- 11 Connor S, Alexakis N, Raraty MG *et al.* Early and late complications after pancreatic necrosectomy. *Surgery* 2005; **137**: 499–505.
- 12 Reddy M, Jindal R, Gupta R, Yadav TD, Wig JD. Outcome after pancreatic necrosectomy: trends over 12 years at an Indian centre. *ANZ J. Surg.* 2006; **76**: 704–9.
- 13 Farkas G, Marton J, Mandi Y, Leindler L. Surgical management and complex treatment of infected pancreatic necrosis: 18-year experience at a single center. *J. Gastrointest. Surg.* 2006; **10**: 278–85.
- 14 Voermans RP, Veldkamp MC, Rauws EA, Bruno MJ, Fockens P. Endoscopic transmural debridement of symptomatic organized pancreatic necrosis (with videos). *Gastrointest. Endosc.* 2007; **66**: 909–16.
- 15 Papachristou GI, Takahashi N, Chahal P, Sarr MG, Baron TH. Peroral endoscopic drainage/debridement of walled-off pancreatic necrosis. *Ann. Surg.* 2007; **245**: 943–51.
- 16 Gardner TB, Chahal P, Papachristou GI *et al.* A comparison of direct endoscopic necrosectomy with transmural endoscopic drainage for the treatment of walled-off pancreatic necrosis. *Gastrointest. Endosc.* 2009; **69**: 1085–94.
- 17 Seifert H, Biermer M, Schmitt W *et al.* Transluminal endoscopic necrosectomy after acute pancreatitis: a multicentre study with long-term follow-up (the GEPARD Study). *Gut* 2009; **58**: 1260–6.
- 18 Parikh PY, Pitt HA, Kilbane M *et al.* Pancreatic necrosectomy: North American mortality is much lower than expected. *J. Am. Coll. Surg.* 2009; **209**: 712–9.
- 19 Cheung MT, Li WH, Kwok PC, Hong JK. Surgical management of pancreatic necrosis: towards lesser and later. *J. Hepatobiliary Pancreat. Sci.* 2010; **17**: 338–44.
- 20 Babu BI, Sheen AJ, Lee SH, O'Shea S, Eddleston JM, Siriwardena AK. Open pancreatic necrosectomy in the multidisciplinary management of postinflammatory necrosis. *Ann. Surg.* 2010; **251**: 783–6.
- 21 Horvath K, Freeny P, Escallon J *et al.* Safety and efficacy of video-assisted retroperitoneal debridement for infected pancreatic collections: a multicenter, prospective, single-arm phase 2 study. *Arch. Surg.* 2010; **145**: 817–25.
- 22 van Santvoort HC, Besselink MG, Bakker OJ *et al.* A step-up approach or open necrosectomy for necrotizing pancreatitis. *N. Engl. J. Med.* 2010; **362**: 1491–502.
- 23 Raraty MG, Halloran CM, Dodd S *et al.* Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. *Ann. Surg.* 2010; **251**: 787–93.
- 24 Beenen E, Brown L, Connor S. A comparison of the hospital costs of open vs. minimally invasive surgical management of necrotizing pancreatitis. *HPB* 2011; **13**: 178–84.
- 25 Varadarajulu S, Phadnis MA, Christein JD, Wilcox CM. Multiple transluminal gateway technique for EUS-guided drainage of symptomatic walled-off pancreatic necrosis. *Gastrointest. Endosc.* 2011; **74**: 74–80.
- 26 Gardner TB, Coelho-Prabhu N, Gordon SR *et al.* Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. *Gastrointest. Endosc.* 2011; **73**: 718–26.
- 27 Bakker OJ, van Santvoort HC, van Brunschot S *et al.* Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA* 2012; **307**: 1053–61.
- 28 Senthil Kumar P, Ravichandran P, Jeswanth S. Case matched comparison study of the necrosectomy by retroperitoneal approach with transperitoneal approach for necrotizing pancreatitis in patients with CT severity score of 7 and above. *Int. J. Surg.* 2012; **10**: 587–92.
- 29 Tong Z, Li W, Yu W *et al.* Percutaneous catheter drainage for infective pancreatic necrosis: is it always the first choice for all patients? *Pancreas* 2012; **41**: 302–5.
- 30 Jurgensen C, Naser F, Boese-Landgraf J, Schuppan D, Stolzel U, Fritscher-Ravens A. Endoscopic ultrasound-guided endoscopic necrosectomy of the pancreas: is irrigation necessary? *Surg. Endosc.* 2012; **26**: 1359–63.
- 31 Bausch D, Wellner U, Kahl S *et al.* Minimally invasive operations for acute necrotizing pancreatitis: comparison of minimally invasive retroperitoneal necrosectomy with endoscopic transgastric necrosectomy. *Surgery* 2012; **152**: S128–34.
- 32 Tan J, Tan H, Hu B *et al.* Short-term outcomes from a multicenter retrospective study in China comparing laparoscopic and open surgery for the treatment of infected pancreatic necrosis. *J. Laparoendosc. Adv. Surg. Tech. A* 2012; **22**: 27–33.
- 33 Gluck M, Ross A, Irani S *et al.* Dual modality drainage for symptomatic walled-off pancreatic necrosis reduces length of hospitalization, radiological procedures, and number of endoscopies compared to standard percutaneous drainage. *J. Gastrointest. Surg.* 2012; **16**: 248–56; discussion 56–7.
- 34 Ulagendra Perumal S, Pillai SA, Perumal S, Sathyanesan J, Palaniappan R. Outcome of video-assisted translumbar retroperitoneal necrosectomy and closed lavage for severe necrotizing pancreatitis. *ANZ J. Surg.* 2014; **84**: 270–4.
- 35 Rana SS, Bhasin DK, Rao C, Gupta R, Singh K. Non-fluoroscopic endoscopic ultrasound-guided transmural drainage of symptomatic non-bulging walled-off pancreatic necrosis. *Dig. Endosc.* 2013; **25**: 47–52.
- 36 Yasuda I, Nakashima M, Iwai T *et al.* Japanese multicenter experience of endoscopic necrosectomy for infected walled-off pancreatic necrosis: The JENIPaN study. *Endoscopy* 2013; **45**: 627–34.
- 37 Bang JY, Wilcox CM, Trevino J *et al.* Factors impacting treatment outcomes in the endoscopic management of walled-off pancreatic necrosis. *J. Gastroenterol. Hepatol.* 2013; **28**: 1725–32.
- 38 Gou S, Xiong J, Wu H *et al.* Five-year cohort study of open pancreatic necrosectomy for necrotizing pancreatitis suggests it is a safe and effective operation. *J. Gastrointest. Surg.* 2013; **17**: 1634–42.
- 39 Premkumar R, Phillips AR, Petrov MS, Windsor JA. The clinical relevance of obesity in acute pancreatitis: targeted systematic reviews. *Pancreatol.* 2015; **15**: 25–33.
- 40 Yashima Y, Isayama H, Tsujino T *et al.* A large volume of visceral adipose tissue leads to severe acute pancreatitis. *J. Gastroenterol.* 2011; **46**: 1213–8.
- 41 Takahashi N, Papachristou GI, Schmit GD *et al.* CT findings of walled-off pancreatic necrosis (WOPN): differentiation from pseudocyst and prediction of outcome after endoscopic therapy. *Eur. Radiol.* 2008; **18**: 2522–9.
- 42 Thoeni RF. The revised Atlanta classification of acute pancreatitis: its importance for the radiologist and its effect on treatment. *Radiology* 2012; **262**: 751–64.
- 43 Morgan DE, Baron TH, Smith JK, Robbin ML, Kenney PJ. Pancreatic fluid collections prior to intervention: evaluation with MR imaging compared with CT and US. *Radiology* 1997; **203**: 773–8.

- 44 Zaheer A, Singh VK, Qureshi RO, Fishman EK. The revised Atlanta classification for acute pancreatitis: updates in imaging terminology and guidelines. *Abdom. Imaging* 2013; **38**: 125–36.
- 45 da Costa DW, Boerma D, van Santvoort HC *et al.* Staged multidisciplinary step-up management for necrotizing pancreatitis. *Br. J. Surg.* 2014; **101**: e65–79.
- 46 Loveday BP, Srinivasa S, Vather R *et al.* High quantity and variable quality of guidelines for acute pancreatitis: a systematic review. *Am. J. Gastroenterol.* 2010; **105**: 1466–76.
- 47 Working Party of the British Society of Gastroenterology; Association of Surgeons of Great Britain and Ireland; Pancreatic Society of Great Britain and Ireland; Association of Upper GI Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. *Gut* 2005; **54** (Suppl 3): iii1–9.
- 48 Banks PA, Freeman ML. Practice guidelines in acute pancreatitis. *Am. J. Gastroenterol.* 2006; **101**: 2379–400.
- 49 Amano H, Takada T, Isaji S *et al.* Therapeutic intervention and surgery of acute pancreatitis. *J. Hepatobiliary Pancreat. Sci.* 2010; **17**: 53–9.
- 50 Gerzof SG, Banks PA, Robbins AH *et al.* Early diagnosis of pancreatic infection by computed tomography-guided aspiration. *Gastroenterology* 1987; **93**: 1315–20.
- 51 Perez A, Whang EE, Brooks DC *et al.* Is severity of necrotizing pancreatitis increased in extended necrosis and infected necrosis? *Pancreas* 2002; **25**: 229–33.
- 52 Buchler MW, Gloor B, Muller CA, Friess H, Seiler CA, Uhl W. Acute necrotizing pancreatitis: treatment strategy according to the status of infection. *Ann. Surg.* 2000; **232**: 619–26.
- 53 Banks PA, Gerzof SG, Langevin RE, Silverman SG, Sica GT, Hughes MD. CT-guided aspiration of suspected pancreatic infection: bacteriology and clinical outcome. *Int. J. Pancreatol.* 1995; **18**: 265–70.
- 54 Rau B, Pralle U, Mayer JM, Beger HG. Role of ultrasonographically guided fine-needle aspiration cytology in the diagnosis of infected pancreatic necrosis. *Br. J. Surg.* 1998; **85**: 179–84.
- 55 Ashley SW, Perez A, Pierce EA *et al.* Necrotizing pancreatitis: contemporary analysis of 99 consecutive cases. *Ann. Surg.* 2001; **234**: 572–9; discussion 9–80.
- 56 Lee JK, Kwak KK, Park JK *et al.* The efficacy of nonsurgical treatment of infected pancreatic necrosis. *Pancreas* 2007; **34**: 399–404.
- 57 van Brunshot S, van Grinsven J, Voermans RP *et al.* Transluminal endoscopic step-up approach versus minimally invasive surgical step-up approach in patients with infected necrotising pancreatitis (TENSION trial): design and rationale of a randomised controlled multicenter trial [ISRCTN09186711]. *BMC Gastroenterol.* 2013; **13**: 161.
- 58 Al-Omran M, Albalawi ZH, Tashkandi MF, Al-Ansary LA. Enteral versus parenteral nutrition for acute pancreatitis. *Cochrane Database Syst. Rev.* 2010; **20**(1): CD002837.
- 59 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.
- 60 Uhl W, Buchler MW, Malferteiner P, Beger HG, Adler G, Gaus W. A randomised, double blind, multicentre trial of octreotide in moderate to severe acute pancreatitis. *Gut* 1999; **45**: 97–104.
- 61 Seta T, Noguchi Y, Shimada T, Shikata S, Fukui T. Treatment of acute pancreatitis with protease inhibitors: a meta-analysis. *Eur. J. Gastroenterol. Hepatol.* 2004; **16**: 1287–93.
- 62 Singh VP, Chari ST. Protease inhibitors in acute pancreatitis: lessons from the bench and failed clinical trials. *Gastroenterology* 2005; **128**: 2172–4.
- 63 Yasunaga H, Horiguchi H, Hashimoto H, Matsuda S, Fushimi K. Effect and cost of treatment for acute pancreatitis with or without gabexate mesylate: a propensity score analysis using a nationwide administrative database. *Pancreas* 2013; **42**: 260–4.
- 64 Takeda K, Takada T, Kawarada Y *et al.* JPN guidelines for the management of acute pancreatitis: medical management of acute pancreatitis. *J. Hepatobiliary Pancreat. Surg.* 2006; **13**: 42–7.
- 65 Yoo JH, Kwon CI, Yoo KH *et al.* Effect of proton pump inhibitor in patients with acute pancreatitis—pilot study. *Korean J Gastroenterol* 2012; **60**: 362–7.
- 66 van Baal MC, van Santvoort HC, Bollen TL, Bakker OJ, Besselink MG, Gooszen HG. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. *Br. J. Surg.* 2011; **98**: 18–27.
- 67 van Brunshot S, Bakker OJ, Besselink MG *et al.* Treatment of necrotizing pancreatitis. *Clin. Gastroenterol. Hepatol.* 2012; **10**: 1190–201.
- 68 Mouli VP, Sreenivas V, Garg PK. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: a systematic review and meta-analysis. *Gastroenterology* 2013; **144**: 333–40.e2.
- 69 Besselink MG, Verwer TJ, Schoenmaeckers EJ *et al.* Timing of surgical intervention in necrotizing pancreatitis. *Arch. Surg.* 2007; **142**: 1194–201.
- 70 Lee VT, Chung AY, Chow PK *et al.* Infected pancreatic necrosis—an evaluation of the timing and technique of necrosectomy in a Southeast Asian population. *Ann. Acad. Med. Singapore* 2006; **35**: 523–30.
- 71 Mofidi R, Lee AC, Madhavan KK, Garden OJ, Parks RW. Prognostic factors in patients undergoing surgery for severe necrotizing pancreatitis. *World J. Surg.* 2007; **31**: 2002–7.
- 72 De Rai P, Zerbi A, Castoldi L *et al.* Surgical management of acute pancreatitis in Italy: lessons from a prospective multicentre study. *HPB* 2010; **12**: 597–604.
- 73 Mainwaring R, Kern J, Schenk WG 3rd, Rudolf LE. Differentiating pancreatic pseudocyst and pancreatic necrosis using computerized tomography. *Ann. Surg.* 1989; **209**: 562–7; discussion 7–8.
- 74 Lecesne R, Taourel P, Bret PM, Atri M, Reinhold C. Acute pancreatitis: interobserver agreement and correlation of CT and MR cholangiopancreatography with outcome. *Radiology* 1999; **211**: 727–35.
- 75 Hirota M, Kimura Y, Ishiko T, Beppu T, Yamashita Y, Ogawa M. Visualization of the heterogeneous internal structure of so-called pancreatic necrosis by magnetic resonance imaging in acute necrotizing pancreatitis. *Pancreas* 2002; **25**: 63–7.
- 76 Arvanitakis M, Delhaye M, De Maertelaere V *et al.* Computed tomography and magnetic resonance imaging in the assessment of acute pancreatitis. *Gastroenterology* 2004; **126**: 715–23.
- 77 Viremouneix L, Monneuse O, Gautier G *et al.* Prospective evaluation of nonenhanced MR imaging in acute pancreatitis. *J. Magn. Reson. Imaging* 2007; **26**: 331–8.
- 78 Ocampo C, Zandalazini H, Kohan G, Silva W, Szlagowsky C, Oria A. Computed tomographic prognostic factors for predicting local complications in patients with pancreatic necrosis. *Pancreas* 2009; **38**: 137–42.