Answering letter

May 3, 2022
Manuscript NO.: 75581
Invasive intervention timing for infected necrotizing pancreatitis: late invasive intervention is not late for collection

Dear Reviewers and Editors,

We are delighted to hear that our manuscript (Manuscript NO.: 75581, Opinion Review) has basically met the publishing requirements of the World Journal of Clinical Cases. On behalf of all authors, I would like to express our sincere appreciation for your constructive comments and correspondence regarding our article entitled "**Invasive intervention timing for infected necrotizing pancreatitis: late invasive intervention is not late for collection**".

Invasive intervention timing for infected necrotizing pancreatitis (INP) is a topic of great interest in the era of minimally invasive. Our views are based on the experience of clinical practices and some results of studies published in recent years. In the present manuscript, we emphasized the principle of late invasive intervention for INP, which seems widely accepted by reviewers. On the other hand, thanks to the reviewer's reminder, we realized that the preferred timing and route for early invasive intervention were also important supplemental information. Based on these professional suggestions, we have revised the manuscript to make it more convincing and hope it could be approval.

A point-by-point response has been prepared as follows, and main changes to the manuscript have been made in bold and blue.
Thank you for your time and effort again.

Yours faithfully
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Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade C (A great deal of language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors have focused on the timing of intervention for infected necrotizing pancreatitis. They have highlighted the need for the current opinion review. They have included the relevant recent trials related to the management of infected necrotizing pancreatitis. While supporting the role of late intervention, authors can include the specific indications for early intervention in infected necrotizing pancreatitis and the preferred route in summary. Also, grammatical errors in the manuscript need to be corrected.

Answering Reviewer：

1. Thank you for your approval and suggestions. we have concluded the specific indications for early intervention in INP which included: patients diagnosed with suspected infected necrosis, and still presented with new-onset or aggravation of organ failure after 48-72hours of antibiotics treatment. For those patients, we prefer percutaneous drainage because it is comparatively handy and can provide rapid source control in most infection lesions.

2. We are sorry for the grammatical errors in the article. After rigorous review, the grammatical or typographical errors have been revised.

Reviewer #2:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This review describes late invasive intervention for infected necrotizing pancreatitis is not late for collection. Please show the results of the literature in a table. Please describe the characteristics of necrotizing pancreatitis that require early intervention.

Answering Reviewer：

1. Thanks for the reminder, we have added a table summarizing the Major randomized controlled trials (RCTs) about the invasive interventions for INP. (See attachment for details)

2. Currently, there is no consensus on the precise characteristics of INP that require early intervention, and if patients got improvement after antibiotics, then the invasive intervention can be postponed for four or more weeks. But occasionally, we will meet cases who are unstable, like new-onset organ failure or aggravation of pre-existed organ failure or persisted organ failure after antibiotics, for these patients, early invasive intervention may be necessary.

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: Dear authors, I liked this manuscript. The topic of the article is very relevant. The requirements for an Opinion Review are generally met. However, the requirements for the references (list all authors and include the PMID and DOI) are not complete.

Answering reviewer:

Thanks for your kind comments, we have modified the reference format as required by the journal. Thanks again for your reminder.

Table 1. Major RCTs guiding the invasive intervention strategies for infected necrotizing pancreatitis

Years	First authors	RCTs	Study group (numbers)	Control group (numbers)	Main Results	Conclusions
2010	Hjalmar C. van Santvoort	PANTER	Step-up approach (n=43, including 41 percutaneous drainage and 2 endoscopic drainages, 24 of them underwent VARD)	Open necrosectomy (n=45, including 44 laparotomies and 1 VARD)	**1.** Major complications or death (40% vs 69%) **2.** New-onset multiple organ failure y (12% vs 40%) **3.** Incisional hernias (7% vs 24%).	A minimally invasive step-up approach, as compared with open necrosectomy, reduced the rate of the composite endpoint of major complications or death among patients with INP.
2012	Olaf J. Bakker	PENGUIN	Endoscopic transgastric necrosectomy (n=10)	Surgical necrosectomy (n=10, including 6 VARDs and 4 laparotomies)	**1.** IL-6 levels increased after surgical necrosectomy, but decreased after endoscopy; **2.** Composite clinical endpoint (20% vs 80%); **3**. New-onset multiple organ (0 vs 50%); **4.** Pancreatic fistulas (10% vs 70%).	Endoscopic necrosectomy reduced the pro-inflammatory response as well as the composite clinical endpoint compared with surgical necrosectomy.
2018	Sandra van Brunschot	TENSION	Endoscopic step-up approach (n=51, including 22 endoscopic drainage only and 27 endoscopic necrosectomies and 2 VARD)	Surgical step-up approach (n=47, including 24 percutaneous drainages only and 23 VARDs)	**1.** Major complications or death during 6-month follow-up (43% vs 45%) **2**. Mortality (18% vs 13%) **3.** Pancreatic fistulas (5% vs 32%) **4**. Hospital stay (35 days vs 65 days).	The endoscopic step-up approach was not superior to the surgical step-up approach in reducing major complications or death. The rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group.
2019	Ji Young Bang	MISER	Endoscopic step-up approach (n=34)	Minimally invasive surgery (n=32, including 26 laparoscopic cystogastrostomy and 6 VARDs)	**1.** Major complications or death (11.8% vs 40.6%); **2.** The rate of SIRS at 72 hours after intervention (20.6% vs 65.6%) **3**. disease-related adverse events (5.9% vs 43.8%); **4.** The average total cost ($75,830 vs $117,492).	An endoscopic transluminal approach for INP, compared with minimally invasive surgery, significantly reduced major complications, lowered costs, and increased quality of life.
2021	L. Boxhoorn	POINTER	Immediate drainage within 24 hours once INP was diagnosed (n=55)	Postponed drainage until the stage of WON (n=49)	**1**. The mean score on the Comprehensive Complication Index (57 vs 58); **2.** Mortality (13% vs 10%) **3.** The mean number of interventions (4.4 vs 2.6).	Immediate drainage did not show superiority over postponed drainage concerning complications. Patients with the postponed-drainage strategy received fewer invasive interventions.

INP for infected necrotizing pancreatitis; VARD for Videoscope assisted retroperitoneal debridement.

Revised Version

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Invasive intervention timing for infected necrotizing pancreatitis: late invasive intervention is not late for collection

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Author contributions: Xiao NJ and Li W contributed to the review design; Xiao NJ wrote the manuscript; Xiao NJ and Cui TT edited the manuscript; Cui TT contributed to the audio core tip; Liu F and Li W contributed to the manuscript revising.

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Abstract:

With the advance of invasive interventions, the treatment model for infected necrotizing pancreatitis has shifted from open surgery to the step-up minimally invasive treatment. Late intervention, originating from the open surgery era, has been questioned in the minimally invasive period. With the emergence of new high-quality evidence about the timing for intervention, it seems to be increasingly apparent that, even in the age of minimal invasiveness, "late intervention" waiting for the necrotic collections to be encapsulated is still necessary. This opinion review mainly discusses the intervention timing for infected necrotizing pancreatitis.

Keywords: [Pancreatitis, Walled-off Necrosis, Minimally Invasive Surgery, Endoscopic Drainage, Endoscopic Gastric Fenestration]

Core tip: Infected necrotizing pancreatitis is a potentially lethal disease that should be identified and managed early. For patients who can be stabilized with antibiotics and supportive care, the invasive treatment, either endoscopic or percutaneous approach, should be delayed for at least four weeks. While patients whose infection cannot be controlled by medication alone may need percutaneous drainage first in 48-72 hours, followed by minimally invasive

surgery (if necessary). Endoscopic gastric fenestration may be performed in selected patients. This innovative alternative intervention should also be postponed to more than four weeks, waiting for the necrosis to mature and the capsular lesions to fuse with the gastric wall.

Introduction

Acute pancreatitis is one of the most common pancreatic diseases. According to the revised Atlanta classification[1], acute pancreatitis is categorized into interstitial edematous and necrotizing pancreatitis. The prognosis of acute edematous pancreatitis is usually favorable. However, acute necrotizing pancreatitis (ANP) is potentially lethal since it has a high ratio of complications. Acute necrotic collection (ANC) and walled-off necrosis (WON) are two main local complications in ANP, arising from pancreatic and/or peripancreatic necrosis in the early and late phases. During the evolution of the disease, they may remain sterile or become infected. Once the infection occurs, as the liquefaction progresses of infected pancreatic necrosis, there may be an increasing amount of suppuration which was described as "pancreatic abscess" in the original Atlanta classification and some old-fashion literature. Since the collections usually contain solid necrotic tissue and the term "pancreatic abscess" was confusing and gradually deprecated.

Currently, "infected necrotizing pancreatitis (INP)" has been preferred to describe ANP with infection. It is more common in severe acute pancreatitis (SAP) and poses a considerable threat with a mortality of up to 30-39%[2]. The treatment of

INP is challenging and usually needs a multidisciplinary team to provide optimal management. Besides, invasive treatment is generally unavoidable. With the advancement of minimally invasive treatment of INP, the therapeutic algorithm has shifted from open surgery to minimally invasive techniques, including percutaneous catheter drainage, per-oral endoscopic drainage or necrosectomy, video-assisted retroperitoneal debridement (VARD), etc. Meanwhile, the invasive intervention timing has been arousing an extensive debate as treatment approaches transform in the minimal invasion era.

Recently, we published a mini-review about pancreatic and peripancreatic collections of acute pancreatitis, in which we mainly discussed treatment approaches [3]. We did not elaborate on the timing for invasive intervention due to space limitations. Another reason was that the results of the POINTER trial[4] had not been published at that time, we did not have direct evidence about this issue, even though we had presumed that the late intervention might be better based on our limited experience. According to the POINTER trail[5], earlier studies, and our limited experience, we have more confidence in late intervention for INP.

1. Diagnosis of infected necrotizing pancreatitis

In ANP, necrosis may involve the pancreatic parenchyma and/or peripancreatic tissues. The pancreatic parenchyma necrosis usually presents as a focal or diffuse area with no enhancement in the arterial and early venous phase. The peripancreatic necrosis is commonly located in the retroperitoneum and lesser

sac, with heterogeneous and ill-defined regions. Both magnetic resonance imaging (MRI) and contrast-enhanced computer tomography (CECT) have a good capability in evaluating the presence and extent of pancreatic and/or peripancreatic necrosis. However, due to the characteristics of short scan duration, accurate severity evaluation, robust reproducibility, and widespread usage, CECT is recommended as the first-line imaging modality for assessing necrosis in ANP[6]. The best timing of execution of CECT is at least 72 hours after symptom onset; otherwise, necrosis may be underestimated or missed.

After necrosis have been evaluated, INP should be suspected if improved patients with systemic inflammatory response syndrome (SIRS) suddenly deteriorate, or SIRS does not improve after two weeks of treatment, or there is evidence of pancreatic peripancreatic gas configurations. Increased serum procalcitonin (PCT) may consolidate the suspicion of infection, while a positive result on Gram stain or culture can diagnose the INP. Nevertheless, the obtaining of sampling, usually by applying fine-needle aspiration (FNA) guided by ultrasound or CT, is invasive. Additionally, the potential contamination and the probability of false-negative and false-positive results of this technique hamper it as a common approach to confirming INP[6]. Therefore, empirical broad-spectrum antibiotics (e.g., carbapenems, quinolones, etc.) can be used as a diagnostic treatment for suspected cases of INP[7]. For patients with clinical deterioration after empirical antibiotic therapy, FNA samples are recommended to be tested to identify the infection for guiding the adjustment of antibiotics.

2. Timing for percutaneous drainage and minimally invasive surgery

As minimally invasive intervention and related clinical studies emerge, the standard treatment of INP has undergone a paradigm shift. The milestone PANTER trial, published in 2010, showed that the minimally invasive step-up approach reduced the rate of major complications or mortality among patients with INP compared to traditional standard open necrosectomy[8], which established the status of the minimally invasive step-up approach as a priority treatment. In this trial, 93% of patients in the step-up approach group received percutaneous catheter drainage as the first step. Furthermore, as shown in the POINTER trial, the postponed-drainage strategy indicated fewer invasive interventions than the immediate-drainage strategy without increasing the incidence of complications. Therefore, whenever possible, the percutaneous drainage should be postponed to about four weeks after the onset of the disease. Moreover, 39% of patients were spared invasive drainage or necrosectomy procedure with this strategy[5].

However, it is not always appropriate to postpone intervention in clinical practice since some cases suffer serious infection which cannot be controlled by medication alone, they usually **demonstrate new-onset organ failure on the basis of SIRS, or present with persistent organ failure even aggravation of pre-existed organ failure.** For these patients, early invasive drainage should be on the agenda. Usually, after an attempt of antibiotic treatment for the first 48-

72hours, we would then prefer percutaneous drainage first, because this approach is comparatively handy and can provide rapid source control in most infection lesions. For adequate drainage, if necessary, the combination of percutaneous drainage and endoscopic drainage can also be considered. Meanwhile, FNA could be done before the indwelling of a drainage catheter to gather the sample, which may provide the details of infection and the antibiotic susceptibility results. If there was no clinical improvement 48-72 hours after the first drainage, another catheter drainage or expanded drainage channel should be constructed. Suppose patients remained no clinical improvement after an additional 48-72 hours, a minimally invasive surgery, for instance, the VARD, should be considered, irrespective of whether the intervention timing exceeded four weeks. If there was a clinical improvement, the minimally invasive surgery could be postponed until the necrosis was substantially or entirely encapsulated.

3. Timing for endoscopic drainage and necrosectomy

In 2012, the PENGUIN trial demonstrated that endoscopic drainage and subsequent necrosectomy (if necessary) reduced the postprocedural proinflammatory response and the composite clinical endpoint compared with percutaneous drainage and subsequent VARD or laparotomy (if necessary) in patients with INP[9]. Despite a small sample size, this was the first randomized controlled trial (RCT) comparing two minimally invasive procedures. Then, another RCT, the TENSION trial with a larger sample size, was published in 2018. Although

this trial did not verify that the endoscopic step-up approach was superior to the surgical step-up approach in reducing major complications or deaths, it demonstrated that the endoscopic step-up approach had a better effect in reducing the incidence of pancreatic fistula and shortening hospital stay[10]. The contemporaneous MISER trial also proved the superiority of the endoscopic approach in reducing fistulas[11]. Meta-analyses based on the RCTs or the other clinical cohort studies confirmed these conclusions[12-14]. Therefore, guidelines recommended the endoscopic step-up approach as a preferred treatment for endoscopically reachable lesions[7].

If patients maintain improvement after antibiotics and other supportive care, then the timing for endoscopic drainage is also recommended to postpone until four or more weeks after initial presentation. As we have mentioned above, the POINTER trial, in which 56% of immediate drainage cases and 67% of postponed drainage cases were intervened with an endoscopic approach, did not show the benefit of early intervention. Besides, compared to the standard timing of endoscopic intervention (⩾4 weeks) in patients with necrotizing pancreatitis, a retrospective study showed that early endoscopic intervention (<4 weeks) had a worse outcome in terms of median hospital days, ICU days, need for rescue open necrosectomy, and the mortality[15]. Another matched case-control study also showed that the total duration of therapy was longer for early intervention compared with the control group[16]. **Moreover, late intervention is related to fewer invasive interventions. For instance, 39% of patients in the postponed**

group in the POINTER trial were treated conservatively with antibiotics and did not require any invasive drainage. Additionally, for patients in the TENSION trial who indicated invasive intervention, under the premise of late invasive intervention (more than 4 weeks after the onset of symptoms), 47% of them only need drainage and were exempt from necrosectomy. We enumerated in Table 1 the major RCTs guiding the invasive intervention strategies for INP to a more convincing recommendation for late endoscopic intervention. These results were consistent with our limited experience, and we usually do not hastily perform the endoscopic drainage in clinical practice until the lesions are encapsulated and the necrotic tissues are partially liquefied. As with the evidence discussed above, this late intervention which usually occurred more than four weeks after the onset of symptoms may have a better drainage outcome. However, in some cases of INP, despite the most outstanding support, the infection may still cause clinical deterioration, requiring invasive intervention earlier. In this situation, we usually prefer the percutaneous drainage as discussed above, and endoscopic drainage will be reserved for those who lack an ideal drainage path or have poor percutaneous drainage effects.

For endoscopic drainage, the most used stents include plastic stents and metal stents. Traditionally, the double pigtail plastic stent with a shape to minimize migration risk was used mostly in drainage. As introduced in the TENSION trial, two 7 French double pigtail stents and an 8.5 French nasocystic catheter were used as a combination for drainage. Due to the small diameter, the plastic stent

is prone to occlusion during the drainage process, making it more suitable for INP with more liquid and less solid necrotic tissue. When the fluid was wholly drained or the stents were blocked, the plastic stents should be opportunely removed. Owing to the larger luminal diameter, metal stent drainage is more effective in patients with INP. Nevertheless, one of its limitations is stent migration. As a result, various metal stents with anti-migration functions have been introduced in recent years. Among them, the most striking one is lumen-apposing metal stent (LAMS). Compared with the plastic stent, LAMS is related to a shorter procedure duration but a higher stent-related adverse event risk[17], including LAMS buried under gastric mucosal, pseudoaneurysms bleeding, and obstructive jaundice. Most of them occurred in patients whose LAMS had been placed for more than three weeks[17]. A retrospective study also observed that patients with LAMS had a higher risk of pseudoaneurysm bleeding[18]. Therefore, it is crucial to retrieve LAMS timely after the drainage purpose is achieved. Currently, a CT scan in 3 weeks is recommended to evaluate the drainage effect followed by LAMS removal to minimize the adverse events[17].

To avoid stent-related complications, we explored endoscopic gastric fenestration (EGF) as an innovative alternative intervention without stents for infected WON[19]. First, endoscopic submucosal dissection (ESD) achieved initial fenestration between the stomach and the WON lesion. Then, under the guidance of endoscopic ultrasound (EUS) and the spatial direction of WON, the fenestration was suitably enlarged to 1.5-3 cm to allow efficient drainage and direct

endoscopic necrosectomy. This approach is not suitable for all WON, since its prerequisite is the fusion of WON with its closely connected stomach wall, which can present as mucosal inflammation such as edema and erosion in the direct endoscopic view and unnormal combined thickness without distinct layers in the EUS view. Therefore, late intervention waiting for the maturity of INP and the fusion of the encapsulated lesion with the gastric wall is also necessary for the EGF.

Conclusion

The endoscopic step-up approach has been recommended as the first-line treatment for patients with INP. With the results of published studies (especially the POINTER trial) and our limited experiences, the late invasive intervention is not late for INPs. In contrast, this delayed invasive intervention strategy may avert the need for invasive intervention in around one-third of patients. In addition, patients with late invasive intervention strategies may get a chance of an innovative EGF treatment, thereby avoiding stent and related complications.

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Table 1. Major RCTs guiding the invasive intervention strategies for infected necrotizing pancreatitis

Years	First authors	RCTs	Study group (numbers)	Control group (numbers)	Main Results	Conclusions
2010	Hjalmar C. van Santvoort	PANTER	Step-up approach (n=43, including 41 percutaneous drainage and 2 endoscopic drainages, 24 of them underwent VARD)	Open necrosectomy (n=45, including 44 laparotomies and 1 VARD)	**1.** Major complications or death (40% vs 69%) **2.** New-onset multiple organ failure y (12% vs 40%) **3.** Incisional hernias (7% vs 24%).	A minimally invasive step-up approach, as compared with open necrosectomy, reduced the rate of the composite endpoint of major complications or death among patients with INP.
2012	Olaf J. Bakker	PENGUIN	Endoscopic transgastric necrosectomy (n=10)	Surgical necrosectomy (n=10, including 6 VARDs and 4 laparotomies)	**1.** IL-6 levels increased after surgical necrosectomy, but decreased after endoscopy; **2.** Composite clinical endpoint (20% vs 80%); **3**. New-onset multiple organ (0 vs 50%); **4.** Pancreatic fistulas (10% vs 70%).	Endoscopic necrosectomy reduced the pro-inflammatory response as well as the composite clinical endpoint compared with surgical necrosectomy.
2018	Sandra van Brunschot	TENSION	Endoscopic step-up approach (n=51, including 22 endoscopic drainage only and 27 endoscopic necrosectomies and 2 VARD)	Surgical step-up approach (n=47, including 24 percutaneous drainages only and 23 VARDs)	**1.** Major complications or death during 6-month follow-up (43% vs 45%) **2**. Mortality (18% vs 13%) **3.** Pancreatic fistulas (5% vs 32%) **4**. Hospital stay (35 days vs 65 days).	The endoscopic step-up approach was not superior to the surgical step-up approach in reducing major complications or death. The rate of pancreatic fistulas and length of hospital stay were lower in the endoscopy group.
2019	Ji Young Bang	MISER	Endoscopic step-up approach (n=34)	Minimally invasive surgery (n=32, including 26 laparoscopic cystogastrostomy	**1.** Major complications or death (11.8% vs 40.6%); **2.** The rate of SIRS at 72 hours after intervention (20.6% vs 65.6%) **3**. disease-related adverse events (5.9% vs 43.8%); **4.** The average total cost ($75,830 vs	An endoscopic transluminal approach for INP, compared with minimally invasive surgery, significantly reduced major complications, lowered costs, and increased quality of life.

				and 6 VARDs)	$117,492).	
2021	L. Boxhoorn	POINTER	Immediate drainage within 24 hours once INP was diagnosed (n=55)	Postponed drainage until the stage of WON (n=49)	**1**. The mean score on the Comprehensive Complication Index (57 vs 58); **2.** Mortality (13% vs 10%) **3.** The mean number of interventions (4.4 vs 2.6).	Immediate drainage did not show superiority over postponed drainage concerning complications. Patients with the postponed-drainage strategy received fewer invasive interventions.

INP for infected necrotizing pancreatitis; VARD for Videoscope assisted retroperitoneal debridement.