Open Access

OBM Hepatology and Gastroenterology

Review

Managing Acute Severe Necrotising Pancreatitis

Michal Kawka, Tamara MH Gall *, Long R Jiao

Department of Surgery and Cancer, Hammersmith Hospital, Du Cane road, London, W12 0HS, UK; E-Mails: michal.kawka17@imperial.ac.uk, tamara.gall1@nhs.net, l.jiao@imperial.ac.uk

* **Correspondence:** Tamara Gall; E-Mail: tamara.gall1@nhs.net

Academic Editor: Prashanth Rawla

Special Issue: Pancreatitis: New Insights into Etiology, Pathogenesis, Diagnosis, Management and Complications

OBM Hepatology and Gastroenterology
2019, volume 3, issue 2
doi:10.21926/obm.hg.1902022

Received: February 25, 2019
Accepted: May 31, 2019
Published: June 05, 2019

Abstract

***Background*:** Severe necrotising pancreatitis (SNP) is characterised by high mortality, severe complications and a poor prognosis despite progress in the understanding of the aetiology and progression of the disease. Traditionally, necrotic changes were removed by open necrosectomy but the paradigm has shifted towards more conservative management and minimally-invasive surgical procedures. However, there is still no consensus on the best management pathway. Minimally-invasive procedures such as percutaneous drainage, endoscopic transluminal necrosectomy, video-assisted retroperitoneal debridement (VARD) and other minimally-invasive surgical variants including percutaneous necrosectomy, as well as step-up protocols (less invasive procedure followed by a more invasive procedure if needed) have all been suggested as potential replacements of open necrosectomy.

***Methods*:** A literature search was conducted in PubMed database to look for comparative studies (RCTs, case series and pooled analyses) between two or more surgical techniques utilised for SNP management. Studies were limited to the last 10 years; retrospective studies were restricted by the number of cases (min. 50). Only management of necrotic collections was taken intro considerations.

***Results*:** Evidence indicates that all minimally invasive surgical options present a viable, non-inferior alternative to open necrosectomy, allowing for reduction in major complications and reduced length of hospital stay. There is no consensus on which minimally-invasive method results in better patient outcomes.

***Conclusions*:** The management of SNP is still dependent on the preference and skill of the clinician and while the evidence base supports the introduction of step-up protocols and less-invasive methods, a higher quality of evidence has to be generated in order to identify groups of patients, who will benefit from a certain type of intervention.

Keywords

Acute severe necrotising pancreatitis; managing

1. Introduction

Acute pancreatitis is a common abdominal emergency with varied aetiologies and a diverse clinical course. Gallstones and alcohol are the main and important causes of acute pancreatitis [1]. Other important causes of AP include hypertriglyceridemia, Post-ERCP, medications, genetic causes and pancreatic duct injury [2-6]. Some rare causes of AP include biliary sludge and microlithiasis, hypercalcemia, infections, biliary obstruction, biliary cysts and idiopathic causes [7] [8-10]. Most of the cases follow a mild or a moderate progression but approximately a third can be classified as severe acute pancreatitis [11, 12]. According to Revised Atlanta Classification severe acute pancreatitis can be defined as acute pancreatitis coexisting with persistent organ failure (>48h) and/or necrotic changes, pseudocysts or abscesses [13]. Multiple criteria such as APACHE II modified Glasgow score, highest recorded level CRP level or BISAP are also commonly used as tools for severity assessment [14]. Amongst patients with necrotic changes, a third develop infected necrosis, which further worsens prognosis, with survival estimated to be between 15-35% in this group [15]. Clinical severity and state of necrotic changes largely affect the management strategy and the decision for surgical intervention compared with conservative management. Infected necrosis is associated with SIRS due to a cytokine storm and can transform into sepsis, ultimately leading to organ failure, which further complicates the management of patients [16]. In order to confirm infected necrosis either fine-needle aspiration (FNA) resulting in positive bacterial culture or contrast-enhanced computerised tomography (CECT) showing gas collections should be performed [17, 18]. Traditionally, confirmed infected necrosis combined with poor clinical state provides an indication for surgical intervention, however currently this notion is being challenged with conservative and minimally-invasive techniques emerging [19].

Historically, open necrosectomy was a surgical management option for necrotising pancreatitis, however, the standards of surgical treatment have changed in recent years, with open surgery giving way to less invasive management options. Currently, there is no consensus on the best approach for severe necrotising pancreatitis (SNP) and the choice is primarily based on the experience of the surgeons, availability of the equipment and preference of the centre [12, 15, 17, 20]. Commonly employed methods include open necrosectomy, percutaneous drainage (PD), endoscopic transluminal necrosectomy (ETN) video-assisted retroperitoneal debridement (VARD) and other minimally-invasive surgical variants including percutaneous necrosectomy [21]. These

surgical options can be used in combinations in so-called 'step-up' approaches when a less invasive procedure (most often drainage) can be followed by a more invasive procedure (VARD, ETN or open necrosectomy) in case of no clinical improvement [22]. The list of techniques is not exhaustive and multiple variations of the aforementioned techniques are employed, as various centres introduce modifications [21, 23].

To date, there have been a few studies aiming to assess the efficacy and comparing the outcomes of those multiple surgical strategies, thus allowing to formulate clear management pathways in severe necrotising pancreatitis. Most of the evidence regarding the management of SNP comes from either case series or retrospective comparative analyses. A general paradigm shift towards less invasive approaches can be observed in recent years, however, there still is a lack of consistent evidence to substantiate it, as some outcomes reported in trials do not always converge. This review aims to present the main available surgical techniques and compare the current methods of severe necrotising pancreatitis management.

2. Methods

A literature search was conducted in PubMed database to find substantial studies related to severe necrotising pancreatitis surgical management from the last 10 years. For the purpose of analysis randomised controlled trials, meta-analysis, pooled analysis of case series and retrospective studies (with more than 50 patients), involving comparisons of surgical methods were taken into consideration. The main focus of this review was comparative studies, highlighting differences between 2 or more surgical techniques. The main studies and their outcomes are highlighted in Table 1. This review focuses on necrotic collections, which can be classified as either walled-off necrosis (WON) or acute necrotic collection (ANC) and does not discuss acute fluid collections (AFC), abscess and pseudocyst management.

3. Management Strategies for Severe Necrotising Pancreatitis (SNP)

3.1 General Management

General management of acute pancreatitis involves aggressive fluid resuscitation, nutritional support and pain management [24]. Traditionally, antibiotics would be given as prophylaxis, however, multiple RTCs have proven, that there is no evidence supporting their use without confirmation of infected necrosis [25, 26]. If sterile necrosis is diagnosed, a conservative management pathway was confirmed to produce fewer complications and be a safe and efficient alternative of management [27]. Although, the absence of infection in necrotic collections does not exclude a severe clinical course (associated with persistent organ failure or rapid clinical deterioration) sterility of necrosis is not an absolute contraindication for surgery in the later phase of the disease [28]. The timing of intervention is an important consideration, that was debated throughout the years, but a literature review suggested that early conservative management with interventions in the later stages provides the best outcomes for patients [29]. Delay in the intervention (approx. 3-5 weeks) allows the necrotic tissue to become liquified and more defined (walled-off), which makes removal easier and more complete [15, 30, 31].

Table 1 Summary of main studies on management of SNP.

Authors and date	Methodology and design	Number of patients	Main findings	Limitations
Hollemans et al. [42] 2019	Long term follows up (mean 86±11 months) of PANTER trial (ref number). Open necrosectomy vs surgical step-up (drainage + VARD)	73 cases (38 in open necrosectomy vs 35 in step-up)	Step-up approach associated with lower rates of incisional hernias (23% vs 53%; p=0.004), endocrine insufficiency (40% vs 64%; p=0.05) and exocrine insufficiecy (29% vs 56%; p=0.03) No significant difference in recurrence of pancreatitis, medical costs, pain and quality of life between groups.	Endocrine insufficiency measured based on the use of anti-diabetic medication. Quality of life questionnaires not collected annually after first year creating a 6-year gap between measurements. Medical costs analysis did not include physiotherapists and other paramedic services.
Woo et al. [48] 2019	Retrospective study. Endoscopic drainage vs. percutaneous drainage	32 cases (20 endoscopic vs 12 percutaneous)	No significant difference in CRP reduction between the groups. HR normalisation (56.0% vs 11.1%, p = 0.0234) and RR normalisation (83.3% vs 0.0%, p = 0.003), as well as post-procedure LOS (27 vs 46 days, p=0.02) in favour of endoscopic drainage.	Retrospective character of the study. Timing of intervention not normalised due to retrospectives of analysis. Small sample size and thus statistical power.
van Brunschot et al. [32] 2018	Randomised control trial. Endoscopic step-up (PD±ETN) vs. surgical step-up (PD±VARD)	98 cases (51 endoscopic step-up vs. 47 surgical step-up)	Surgical step-up associated with 32% of pancreatic fistula compared to 5% in endoscopic-step-up (p< 0.01). Reduction in mean hospital stay by 13 days in endoscopic step-up (p<0.02). No statistically significant difference in mortality.	Only 6-month follow-up on the lengths of stay in the hospital, additional PD following ETN in endoscopic step up for 2/3 of patients.
van Brunschot et al. [46] 2018	Pooled analysis of retrospective studies. Open necrosectomy vs minimally-invasive surgery (ETN or VARD)	1980 cases (1167 open necrosectomy vs. 813 minimally-invasive)	Lower mortality for both minimally-invasive techniques (OR=0.53, p=0.006 for VARD and OR=0.20, p=0.006 for ETN). After stratification and matching of the cases similar results obtained in high-risk and very-high risk groups.	Heterogeneity of methodologies within the analysed cohorts. Data not adjusted for year of necrosectomy in multivariate analysis. Lack of radiological data regarding location of necrotic collections.

Wronski et al. [20] 2016	Retrospective paired study; open necrosectomy vs step-up (PD±MARPN)	70 cases (48 step-up vs. 22 open necrosectomy)	Mortality comparable in both groups. Length of ICU stay ($p<0.05$) and new onset organ failure ($p<0.02$) lower in step-up group.	Retrospective character of the study and selection bias. Minimally invasive procedures relatively new for surgical team. Low statistical power for mortality comparison due to moderate number of patients.
Rasch et al. [37] 2016	Retrospective multicentre analysis. Step-up (drainage±minimally-invasive surgery) vs. open necrosectomy	220 cases (190 step-up vs 30 open necrosectomy)	Lower major complications (45% vs 73%, $p<0.001$) and mortality (10% vs 33%, $p=0.002$) for the step-up group. Length of stay in the hospital without statistically significant difference.	Retrospective character of the study. Inequality in number of patinates in two groups. Insufficient data to asses severity of the pancreatitis due to heterogeneity in data collection between the centres.
Bang et al. [57] 2014	Observational study. Endoscopic drainage±ETN vs. algorithmic approach (endoscopic drainage/PD/ETN/per cutaneous necrosectomy/open necrosectomy)	100 cases (47 with endoscopic drainage±ETN vs. 53 with algorithmic approach)	Algorithmic approach had 91% success rate compared to endoscopic drainage group, which had 60% success rate ($p<0.001$).	Observational study, arbitrary criteria in the algorithm, referral bias.
Guo et al. [33] 2013	Retrospective study. Open necrosectomy vs retroperitoneal necrosectomy	412 cases (304 open necrosectomy vs 108 retroperitoneal necrosectomy)	Lower mortality rates (8.3% vs 20.4%, $p=0.004$), complications rates ($p <0.05$) and length of hospital stay (30 vs. 48 days, $p < 0.05$) in the retroperitoneal necrosectomy group.	Retrospective character of the study. Decision for retroperitoneal necrosectomy based on location of necrotic collection. Selection bias in the retroperitoneal necrosectomy group.

Bakker et. al [34] 2012	Randomised control trial. VARD vs ETN	22 cases (10 ETN vs. 10 VARD; 2 excluded from analysis).	ETN reduced major complications or death (p=0.03) and pro-inflammatory IL-6 levels post-surgery (p=0.004)	Small sample size.
Tu et al. [35] 2012	Retrospective study. Open necrosectomy vs MARPN (*VARD)	50 cases (32 open necrosectomy vs. 18 MARPN)	Lower complication rate in MARPN group (27.8% vs. 43.8%). Reduced length of hospital stay in the minimally-invasive group (130 vs 148 days, p=0.007)	Retrospective character of the study. Deviation from VARD technique.
Gluck et al. [36] 2012	Retrospective study. PD vs PD + Endoscopic drainage	94 cases (45 PD vs. 49 PD+endoscopic drainage)	Longer mean hospital stay (54 vs. 24, $p < 0.002$) in the PD only group.	Non-randomised retrospective study, differences in baseline characteristics between groups. Selection bias.
van Stantvoort et al. [38] 2010	Randomised control trial. Open necrosectomy vs surgical step-up (drainage + VARD)	88 cases (45 open necrosectomy vs 43 surgical step-up)	Reduced major complications and/or mortality in step-up group; 0.57 RR, p=0.006. New-onset multiple-organ failure occurred less often in patients as- signed to the step-up approach than in those assigned to open necrosectomy (12% vs. 40%, p=0.002). Difference in mortality not statistically significant.	Small sample size makes the study not designed for mortality assessment.
Raraty et al. [52] 2010	Retrospective study. Open necrosectomy vs MARPN (*VARD)	189 cases (52 open necrosectomy vs. 137 VARD)	Higher incidence of MOF (56% vs. 31%, p< 0.0001) in open necrosectomy group. Higher mortality (38% vs. 19%, p=0.009) and postoperative complications (81% vs. 55%, p = 0.001) rates in open necrosectomy groups.	Retrospective character of the study.

3.2 Outcomes and Complications

Most commonly in the studies either mortality and/or major postoperative complications constitute the primary outcome (often in form of a composite outcome). Common complications include pancreatic fistula, haemorrhage, sepsis, new onset organ failure and type 3c diabetes, as well as incisional hernias and infection of the wound [20, 32, 33, 34, 35, 36]. Secondary outcomes include the length of hospital stay, length of ICU stay, number of interventions performed and the cost of overall patient management [32-38]. Some studies also include the number of reoperations, utilisation of healthcare recourses and readmissions as outcomes [38].

3.3 Open Necrosectomy

Traditionally open necrosectomy (or debridement) was indicated for the management of SNP. This technique involves a longitudinal midline abdominal incision that allows full access to the lesser sac in order for necrosis removal and lavage, as well as assessment of the abdominal cavity [23]. The operative technique has four main variations that differ in wound management and the need for planned reoperations including: necrosectomy combined with open packing; planned staged relaparotomies with repeated lavage; closed continuous lavage of the lesser sac; and closed packing [23]. The rationale behind this technique is to achieve maximal preservation of healthy pancreatic parenchyma combined with the removal of necrosis and debris due to a big operation field, thus good access to collection in all regions of the pancreas. However, since less-invasive techniques were introduced open necrosectomy has been replaced in many centres as the primary intervention. It was noted that this method generates multiple complications including the creation of pancreatic fistulas, gastric outlet obstruction syndrome and incisional hernia, all of which contribute to need of reoperations and therefore increase the length of hospital stay and healthcare utilisation [39-41]. Moreover, major abdominal surgery provides additional stress to severely unwell patients which is thought to be one of the reasons for high mortality rates in this patient group [32].

In recent years, this paradigm was challenged in multiple trials comparing open necrosectomy with novel, minimally-invasive methods. In a pooled retrospective analysis van Brunschot et al. have concluded that the use of minimally invasive techniques (ETN or VARD) results in lower mortality in all patients analysed but more importantly in very-high and high-risk patient groups after stratification [32]. Moreover, an RCT by van Stantvoort showed lower rates of major complications and new onset organ failure, when step-up approaches were compared to open necrosectomy [38]. Recently, a follow-up of said randomised clinical trial was conducted by Hollemans et al. and showed that long-term complication rates can be reduced by using step-up approach (compared to open necrosectomy), although no significant differences in medical costs and quality of life was found [42].

3.4 Percutaneous Drainage (PD)

Percutaneous catheter drainage was introduced as one of the first minimally-invasive options of SNP management options around 2000 [43). The procedure involved insertion of a catheter either via the retroperitoneal approach or via the anterior transabdominal route depending on the location and size of the necrosis [43). The drain can be inserted either using a free-hand technique

or under US or CT guidance and multiple drains might be utilised to provide the optimal level of drainage (44). Nowadays, PD is often used as the primary option, preferred by clinicians due to its relative non-invasiveness. Drainage allows for clinical improvement of the patient and therefore contributes to the delay of possibly more invasive surgical procedure, which is desirable if the surgical debridement is planned [44]. A variation of this technique is endoscopic drainage, which also can be used as a primary intervention or part of the step-up protocols [45].

PD in multiple studies has a success rate of 30-50% as a primary intervention [32, 46]. Its failure is most commonly attributed to the inability of the catheter to remove solid debris, (preventing improvement of the clinical status of patient), as well as the size of necrotised tissue, heterogeneity of collection and MOF [31, 44, 47]. PD was shown to be an effective first intervention of the step-up protocols, reducing major postoperative complications [38]. A study by Gluck et al. has also shown that a combination of both endoscopic and percutaneous drains has a potential to decrease the length of hospital stay [36]. Woo et al. have compared endoscopic and percutaneous drainage and found that endoscopic drainage is associated with shorter post-procedure length of hospital stay, as well as higher rates of SIRS-related parameter normalisation, although with no significant difference in CRP levels and WCC normalisation [48]. In 2015 study, Stahl et al. have suggested using a U-tube catheter aimed at reduction of drain obstruction, fistula formation, more effective flushing and reduction of resource utilisation; preliminary results showed potential of this variant of PD [49].

3.5 Videoscope-Assisted Retroperitoneal Approach (VARD)

This variant of necrosectomy utilises a retroperitoneal approach, through the left lumbar region to access the pancreas [50]. The use of video-assistance allows for the incision size to be reduced, thus minimising the trauma of surgery. A small percutaneous route toward the necrotic collection is established, which is then dilated to allow for full lavage and debridement [51]. A variation of VARD which is also used is Minimal Access Retroperitoneal Pancreatic Necrosectomy (MARPN); it does not utilise camera assistance but follows the same principle, as far as debridement is concerned [20, 52]. Similar to ETN and VARD, the choice for this method is predominantly determined by the location of the necrotic collection [53]. The efficacy of this technique is still relatively unexplored in major trials or retrospective analyses. Using a retroperitoneal approach allows for a clear pathway to the necrosis. VARD is quoted to be superior over open necrosectomy due to a reduced number of post- and intraoperative complications and generating smaller inflammatory response in the organism following the procedure [52, 38]. The critics have noted that a retroperitoneal approach is suitable only for certain locations of necrotic changes within the pancreas and hence cannot be utilised universally [45].

When directly compared with open necrosectomy, Raraty et al., Tu et al. and Guo et al. in their retrospective studies all found VARD and other minimally invasive surgical techniques to be associated with lower major complications rates and reduced length of hospital stay [52, 35, 33]. Moreover, an RCT by van Santvoort et al. showed VARD compared to open necrosectomy in surgical step-up protocols, was associated with a reduction in new onset organ failure and mortality (although the study was underpowered for mortality analysis) [38].

3.6 Endoscopic Transluminal Necrosectomy (ETN)

ETN is a technique that involves necrosectomy using an endoscope that is introduced into the necrotic collection via either transgastric or transduodenal (depending on the location of the necrotic changes) approach. It alleviates the risks of either open or surgical intervention. A flexible endoscope is passed transorally and then transmurally to perform a puncture of either the stomach or duodenum wall, to gain access to the necrosis [54, 55]. Usually multiple procedures are needed to achieve a full debridement using this approach [30, 34]. This method has been compared to other necrosectomy techniques and has, similarly to VARD, allowed for a reduction of major complications when compared with open necrosectomy. Moreover, a small randomised controlled trial by Bakker et al. has associated ETN with reduced complication rates and lower levels of pro-inflammatory mediators (IL-6) when compared to VARD [34]. This is further confirmed by the study by van Brunschot et al., in which ETN was compared to VARD as a part of a step-up protocol (PD±ETN or PD±VARD) and was associated with reduced mean hospital stay and reduced complication rates [32].

3.7 Step-up Approaches

Step-up protocols are the most recent idea in the development of management strategies for SNP and have been already included in several major guidelines [13, 17, 56]. Their main premise is to use a less invasive technique first (in most cases drainage) and follow it by a more invasive intervention only if needed (ETN, VARD). The efficacy of 'step-up' protocols was investigated in the PANTER study in 2010 and since then multiple step-up protocols were suggested and investigated [38]. When compared with open necrosectomy, step-up reduces the length of hospital stay [20, 37]. The reports on reduced mortality are variable but generally step-up performs better or non-inferiorly compared to open necrosectomy [20, 32, 37, 38]. In his 2014 study, Bang et al. compared an endoscopic step-up procedure with an 'algorithmic' approach, which (based on certain patient criteria) assessed the most suitable intervention and found that the algorithmic approach outperformed standardised step-up protocols with a success rate of 91% to 60% [57].

4. Discussion

This review presents an overview of evidence about the management of acute severe necrotising pancreatitis. There is no unified management strategy, as there is a lack of a reliable predictive tool for clinical progression of necrotising pancreatitis. The choice of intervention is based on the preference of the clinician, availability of equipment and preference of the institution. There is significant heterogeneity in the methodologies used within procedures, with the majority of the studies not specifying which subtype of a certain technique was used, which partially hinders the ability to objectively analyse the outcomes. Moreover, the management of SNP patients is limited to specialised tertiary centres, from where most of the research output comes, which might contribute to an overestimation of success rate, had the more complex method been applied by other surgical teams; some teams in their case reports achieve significantly higher complications and mortality rates when compared to more renounced centres [20]. Multiple studies suggest that the trend of moving towards less invasive surgical methods is associated with lower rates of major complications and mortality rate. Having said that, most of

the studies lack statistical power to showcase mortality reductions significantly. It is also worth noting that while the differences in mortality are not always substantial, multiple studies have shown that less invasive approaches reduce the length of hospital/ICU stay and hence the costs of patient management.

All of the minimally-invasive techniques (whether as primary interventions or within step-up protocols) present as therapeutically viable options. It should be noted, however, that in comparison to open necrosectomy, both ETN and VARD require a higher level of surgical experience and in selected cases might not allow the best access to the necrotic collection. A considerable fraction of the patients was escalated to open necrosectomy in several case series, which emphasises the importance of open necrosectomy in management, despite more novel approaches being available. In our opinion, the current state of evidence supports the development of more formalised step-up protocols and their utilisation to limit major post-surgical complications, but it is still unclear what predicting factor could be used to determine which group of patients will benefit with more radical and invasive procedures. While research proves PD, VARD and ETN, as well as percutaneous necrosectomy as being viable options, the choice between them still remains unsubstantiated by evidence.

One of the biggest limitations of performing analysis is the current state of evidence of surgical management of SNP. Firstly, due to use of variable criteria, pancreatitis can be classified as severe according to several different metrics, thus some studies only had a proportion of patients with severe cases and some patients in the milder stages (14). This problem is also potentiated by the retrospective character of most of the studies and the lack of severity data collection. Secondly, most of the data related to open necrosectomy is from the 1990s and early 2000s, which in light of improved standards of ICU care and changes in pancreatitis management has reduced validity of comparison. Finally, due to the low incidence of severe necrotising pancreatitis and management being confined to tertiary referral centres, it is hard to plan randomised controlled trials with big sample sizes; most of the evidence comes from retrospective analyses which have an in-built bias.

5. Conclusions

In conclusion, current surgical management of severe necrotising pancreatitis is dependent more on preference and expertise of the clinician than reliable evidence. In our opinion, more robust evidence base is needed in order to comprehensively assess efficacy of less-invasive management methods in reducing mortality and identify patient subgroups benefiting from particular interventions in order to establish formalised step-up protocols.

Author Contributions

These authors contributed equally to this work.

Competing Interests

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. No writing assistance was utilized in the production of this manuscript.

References

1. Zillo MB, Eyff TF, Azeredo-Da-Silva ALF, Bersch VP, AB Osvaldt. A systematic review and meta-analysis of the aetiology of acute pancreatitis. HPB. 2019; 21: 259-267.
2. Rawla P, Sunkara T, Thandra KC, Gaduputi V. Hyperglycaemia-induced updated review of current treatment and preventive strategies. Clin J Gastroenterol. 2018; 11: 441-448.
3. Kahaleh M, Freeman M. Prevention and management of post-endoscopic retrograde cholangiopancreatography complications. Clin Endosc. 2012; 45: 305-12.
4. Rawla P, Raj JP. Doxycycline-induced acute pancreatitis: A rare adverse event. Gastroenterology Res. 2017; 10: 244-246.
5. Rosendhal J, Witt H, Szmola R, Bhatia E, Ózsvári B, Landt O, et al. Chymotrypsin C (CTRC) variants that diminish activity or secretion are associated with chronic pancreatitis. Nat Genet. 2008; 40: 78-82.
6. Gerson LB, Tokar J, Chiorean M, Lo S, Decker GA, Cave D, et al. Complications associated with double balloon enteroscopy at nine US centers. Clin Gastroenterol Hepatol. 2009; 7: 1177-1182.e3.
7. Ko CW, Sekijima JH, Lee SP. Biliary sludge. Ann Intern Med. 1999; 16: 301-311.
8. Khoo TK, Vege SS, Abu-Lebdeh HS, Ryu E, Nadeem S, Wermers RA. Acute pancreatitis in primary hyperparathyroidism: A population-based study. J Clin Endocrinol Metab. 2009; 94: 2115-2118.
9. Rawla P, Bandaru SS, Vellipuram AR. Review of infectious etiology of acute pancreatitis. Gastroenterology Res. 2017; 10: 153-158.
10. Jalaly NY, Jalaly NY, Moran RA, Fargahi F, Khashab MA, Kamal A, et al. An evaluation of factors associated with pathogenic PRSS1, SPINK1, CTFR, and/or CTRC genetic variants in patients with idiopathic pancreatitis. Am J Gastroenterol. 2017; 112: 1320-1329.
11. Zerem E. Treatment of severe acute pancreatitis and its complications. World J Gastroenterol. 2014; 20: 13879-13892.
12. Portelli M, Jones CD. Severe acute pancreatitis: pathogenesis, diagnosis and surgical management. Hepatobiliary Pancreat Dis Int. 2017; 16: 155-159.
13. Banks PA, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, et al. Classification of acute pancreatitis--2012: Revision of the atlanta classification and definitions by international consensus. Gut. 2013; 62: 102-111.
14. Khanna AK, Meher S, Prakash S, Tiwary SK, Singh U, Srivastava A, et al. Comparison of ranson, glasgow, MOSS, SIRS, BISAP, APACHE-II, CTSI Scores, IL-6, CRP, and procalcitonin in predicting severity, organ failure, pancreatic necrosis, and mortality in acute pancreatitis. HPB Surg. 2013; 2013: 367581.
15. van Dijk SM, Hallensleben NDL, van Santvoort HC, Fockens P, van Goor H, Bruno MJ, et al. Acute pancreatitis: Recent advances through randomised trials. Gut. 2017; 66: 2024-2032.
16. Bhatia M, Neoptolemos JP, Slavin J. Inflammatory mediators as therapeutic targets in acute pancreatitis. Curr Opin Investig Drugs. 2001; 2: 496-501.
17. 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: iii1-9.

18. Lankisch PG, Apte M, Banks PA. Acute pancreatitis. Lancet. 2015; 386: 85-96.
19. Tenner S, Baillie J, DeWitt J, Vege SS. American college of gastroenterology guideline: Management of acute pancreatitis. Am J Gastroenterol. 2013; 108: 1400-1415.
20. Wronski M, Cebulski W, Witkowski B, Jankowski M, Klucinski A, Krasnodebski IW, et al. Comparison between minimally invasive and open surgical treatment in necrotizing pancreatitis. J Surg Res. 2017; 210: 22-31.
21. Sorrentino L, Chiara O, Mutignani M, Sammartano F, Brioschi P, Cimbanassi S. Combined totally mini-invasive approach in necrotizing pancreatitis: A case report and systematic literature review. World J Emerg Surg. 2017; 12: 16.
22. Besselink MG, van Santvoort HC, Nieuwenhuijs VB, Boermeester MA, Bollen TL, Buskens E, et al. Minimally invasive 'step-up approach' versus maximal necrosectomy in patients with acute necrotising pancreatitis (PANTER trial): Design and rationale of a randomised controlled multicenter trial [ISRCTN13975868]. BMC Surg. 2006; 6: 6.
23. Vasiliadis K, Papavasiliou C, Al Nimer A, Lamprou N, Makridis C. The role of open necrosectomy in the current management of acute necrotizing pancreatitis: A review article. ISRN Surg. 2013; 2013: 579435.
24. Banks PA. Practice guidelines in acute pancreatitis. Am J Gastroenterol. 1997; 92: 377-386.
25. Maravi-Poma E, Gener J, Alvarez-Lerma F, Olaechea P, Blanco A, Dominguez-Munoz JE, et al. Early antibiotic treatment (prophylaxis) of septic complications in severe acute necrotizing pancreatitis: a prospective, randomized, multicenter study comparing two regimens with imipenem-cilastatin. Intensive Care Med. 2003; 29: 1974-1980.
26. Dellinger EP, Tellado JM, Soto NE, Ashley SW, Barie PS, Dugernier T, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis: A randomized, double-blind, placebo-controlled study. Ann Surg. 2007; 245: 674-683.
27. van Santvoort HC, Bakker OJ, Bollen TL, Besselink MG, Ahmed Ali U, Schrijver AM, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. Gastroenterology. 2011; 141: 1254-1263.
28. 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: 619-626.
29. Besselink MG, Verwer TJ, Schoenmaeckers EJ, Buskens E, Ridwan BU, Visser MR, et al. Timing of surgical intervention in necrotizing pancreatitis. Arch Surg. 2007; 142: 1194-1201.
30. Shah A, Denicola R, Edirisuriya C, Siddiqui AA. Management of inflammatory fluid collections and walled-off pancreatic necrosis. Curr Treat Options Gastroenterol. 2017; 15: 576-586.
31. Mortele KJ, Girshman J, Szejnfeld D, Ashley SW, Erturk SM, Banks PA, et al. CT-guided percutaneous catheter drainage of acute necrotizing pancreatitis: clinical experience and observations in patients with sterile and infected necrosis. AJR Am J Roentgenol. 2009; 192: 110-116.
32. van Brunschot S, van Grinsven J, van Santvoort HC, Bakker OJ, Besselink MG, Boermeester MA, et al. Endoscopic or surgical step-up approach for infected necrotising pancreatitis: A multicentre randomised trial. Lancet. 2018; 391: 51-58.
33. Guo Q, Lu H, Hu W, Zhang Z. A retroperitoneal approach for infected pancreatic necrosis. Scand J Gastroenterol. 2013; 48: 225-230.

34. Bakker OJ, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: A randomized trial. JAMA. 2012; 307: 1053-61.
35. Tu Y, Jiao H, Tan X, Sun L, Zhang W. Laparotomy versus retroperitoneal laparoscopy in debridement and drainage of retroperitoneal infected necrosis in severe acute pancreatitis. Surg Endosc. 2013; 27: 4217-4223.
36. Gluck M, Ross A, Irani S, Lin O, Gan SI, Fotoohi M, 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: 248-256.
37. Rasch S, Phillip V, Reichel S, Rau B, Zapf C, Rosendahl J, et al. Open surgical versus minimal invasive necrosectomy of the pancreas-A retrospective multicenter analysis of the german pancreatitis study group. PLoS One. 2016; 11: e0163651.
38. van Santvoort HC, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. N Engl J Med. 2010; 362: 1491-1502.
39. Bassi C, Butturini G, Falconi M, Salvia R, Frigerio I, Pederzoli P. Outcome of open necrosectomy in acute pancreatitis. Pancreatology. 2003; 3: 128-132.
40. Rau B, Bothe A, Beger HG. Surgical treatment of necrotizing pancreatitis by necrosectomy and closed lavage: Changing patient characteristics and outcome in a 19-year, single-center series. Surgery. 2005; 138: 28-39.
41. Chang YC. Is necrosectomy obsolete for infected necrotizing pancreatitis? Is a paradigm shift needed? World J Gastroenterol. 2014; 20: 16925-16934.
42. Hollemans RA, Bakker OJ, Boermeester MA, Bollen TL, Bosscha K, Bruno MJ, et al. Superiority of step-up approach vs open necrosectomy in long-term follow-up of patients with necrotizing pancreatitis. Gastroenterology 2019; 156: 1016-1026.
43. Carter CR, McKay CJ, Imrie CW. Percutaneous necrosectomy and sinus tract endoscopy in the management of infected pancreatic necrosis: An initial experience. Ann Surg. 2000; 232: 175-180.
44. van Baal MC, van Santvoort HC, Bollen TL, Bakker OJ, Besselink MG, Gooszen HG, et al. Systematic review of percutaneous catheter drainage as primary treatment for necrotizing pancreatitis. Br J Surg. 2011; 98: 18-27.
45. Horvath K, Freeny P, Escallon J, Heagerty P, Comstock B, Glickerman DJ, 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: 817-825.
46. van Brunschot S, Hollemans RA, Bakker OJ, Besselink MG, Baron TH, Beger HG, et al. Minimally invasive and endoscopic versus open necrosectomy for necrotising pancreatitis: A pooled analysis of individual data for 1980 patients. Gut. 2018; 67: 697
47. Hollemans RA, Bollen TL, van Brunschot S, Bakker OJ, Ahmed Ali U, van Goor H, et al. Predicting success of catheter drainage in infected necrotizing pancreatitis. Ann Surg. 2016; 263: 787-92.
48. Woo S, Walklin R, Ackermann T, Lo SW, Shilton H, Pilgrim C, et al. Comparison of endoscopic and percutaneous drainage of symptomatic necrotic collections in acute necrotizing pancreatitis. Asian J Endosc Surg. 2019; 1: 88-94.

49. Stahl CC, Moulton J, Vu D, Ristagno R, Choe K, Sussman JJ, et al. Routine use of U-tube drainage for necrotizing pancreatitis: A step toward less morbidity and resource utilization. Surgery. 2015; 158: 919 – 928.
50. van Santvoort HC, Besselink MG, Horvath KD, Sinanan MN, Bollen TL, van Ramshorst B, et al. Videoscopic assisted retroperitoneal debridement in infected necrotizing pancreatitis. HPB (Oxford). 2007; 9: 156-159.
51. Bugiantella W, Rondelli F, Boni M, Stella P, Polistena A, Sanguinetti A, et al. Necrotizing pancreatitis: A review of the interventions. Int J Surg. 2016; 28:S163-S171.
52. Raraty MG, Halloran CM, Dodd S, Ghaneh P, Connor S, Evans J, et al. Minimal access retroperitoneal pancreatic necrosectomy: improvement in morbidity and mortality with a less invasive approach. Ann Surg. 2010; 251: 787-793.
53. Logue JA, Carter CR. Minimally invasive necrosectomy techniques in severe acute pancreatitis: Role of percutaneous necrosectomy and video-assisted retroperitoneal debridement. Gastroenterol Res Pract. 2015; 2015: 693040.
54. van Brunschot S, Fockens P, Bakker OJ, Besselink MG, Voermans RP, Poley JW, et al. Endoscopic transluminal necrosectomy in necrotising pancreatitis: a systematic review. Surg Endosc. 2014; 28: 1425-1438.
55. Hackert T, Buchler MW. Decision making in necrotizing pancreatitis. Dig Dis. 2016; 34: 517-524.
56. Pezzilli R, Zerbi A, Campra D, Capurso G, Golfieri R, Arcidiacono PG, et al. Consensus guidelines on severe acute pancreatitis. Dig Liver Dis. 2015; 47: 532-543.
57. Bang JY, Holt BA, Hawes RH, Hasan MK, Arnoletti JP, Christein JD, et al. Outcomes after implementing a tailored endoscopic step-up approach to walled-off necrosis in acute pancreatitis. Br J Surg. 2014; 101: 1729-1738.