Can infected pancreatic necrosis really be managed conservatively?

Bilal Al-Sarireh, Nicholas G. Mowbray, Ali Al-Sarira, David Griffith, Timothy H. Brown and Toby Wells

Objectives Guidelines advocate minimally invasive drainage rather than open surgery for infected pancreatic necrosis (IPN) after acute pancreatitis. We hypothesized that the conservative approach could be extended even further by treating patients using an antibiotics-only protocol.

Patients and methods Between June 2009 and July 2017, patients with IPN were selectively managed with carbapenem antibiotics for a minimum of 6 weeks. We compared these patients with patients who underwent minimal access retroperitoneal pancreatic necrosectomy (MARPN) for IPN to identify characteristics of this patient group.

Results Of 33 patients with radiologically proven IPN, 13 patients received antibiotics without any surgical or radiological intervention and resulted in no disease-specific mortality and one case of pancreatic insufficiency. In comparison, 44 patients underwent MARPN with a mortality of 20%, and 81.8% developed pancreatic insufficiency. The modified Glasgow score and computed tomography severity score was less in the antibiotic-only group ($P < 0.001$ and $P = 0.014$, respectively). Patients who underwent MARPN had lower serum haemoglobin and albumin levels ($P = 0.030$ and 0.001, respectively), and a higher C-reactive protein ($P = 0.027$).

Conclusion Conservative treatment of IPN with antibiotics is a valid management option for haemodynamically stable patients experiencing less severe disease, requiring careful selection by experienced clinicians. Eur J Gastroenterol Hepatol 30:1327–1331

Introduction

The first classifications of acute pancreatitis (AP) were made by the Boston surgeon Reginald Fritz [1]. His own views on the benefits of surgery in this condition fluctuated, but after 125 years, the medical profession has eventually arrived on a consensus; surgical procedures should be reserved for the most severe form of the disease, namely infected pancreatic necrosis (IPN) [2]. This lethal complication manifests in ~6% of patients with AP and harbours a mortality of 32% [3,4].

Because of the spectrum of severity, the current management strategy for the complications of AP, such as acute necrotic and acute peri-pancreatic collections, should follow the 'step-up' approach [5,6]. Interventions should be delayed for at least 4 weeks from the onset of symptoms to allow for capsule formation. This approach avoids over treatment and has significantly reduced mortality [7]. The primary intervention in the treatment algorithm should be an image-guided, percutaneous drain and then progress to minimally invasive necrosectomy if required. Open debridement should be reserved for patients who continue to deteriorate despite the previous measures [6].

Among the many published reviews and guidelines concerning IPN, there are sporadic reports of cases having resolved without drainage of the collection [5]. This appears to go against surgical principals and yet there have been a number of good outcomes [8,9]. On the basis of these cases, the primary author (B.A.) hypothesized that a cohort of patients with IPN could be treated using a truly conservative treatment approach in our institution. The objective of this study was, therefore, to present a management algorithm for the conservative treatment of IPN, and to define the patient group in the context of all patients with IPN.

Patients and methods

The Pancreatic Unit for South Wales provides specialist care for a population of 2.3 million across five hospitals. This area deals with ~1180 admissions per year with AP, with most being managed locally, according to the British Society of Gastroenterology UK guidelines [10–12]. Referral to the tertiary centre is only if complications of AP are detected and can result in treatment advice or transfer to the specialist pancreatic unit.

Patients across the referral network did not receive antibiotics prophylactically; they were reserved for patients with signs of sepsis [13]. IPN was diagnosed according to the revised Atlanta guidelines by the presence of extra-luminal peri-pancreatic gas with associated hypoperfusion of the pancreas on contrast-enhanced computed tomography (CT) [14]. Once diagnosed, patients were selected for a conservative treatment option if they had less than two organ dysfunction

European Journal of Gastroenterology & Hepatology 2018, 30:1327–1331

Keywords: acute pancreatitis, antibiotic, infected pancreatic necrosis, necrosectomy, pancreatic necrosis

Department of General Surgery, ABM University Health Board, Swansea, UK

Correspondence to Bilal Al-Sarireh, MBBCh, FRCS, PhD, Department of General Surgery, ABM University Health Board, Swansea SA6 6NL, UK

Tel: +44 179 248 7418; fax: +44 179 270 3224;
e-mail: bilal.al-sarireh@wales.nhs.uk

A preliminary version of the patient series was presented to the Association of Surgeons of Great Britain and Ireland Annual conference in Manchester, April 2015.

Received 4 April 2018 **Accepted** 28 May 2018

and did not clinically deteriorate during antibiotic therapy. Organ dysfunction was defined as systolic blood pressure of less than 90 mmHg, oxygen saturation of less than 90%, urine output of less than 0.5 ml/kg for 6 h, serum creatinine of at least 1.5 times baseline or reduced consciousness.

Intravenous carbapenem antibiotics were the preferred antibiotics for IPN because of their pancreatic tissue penetration. Specifically, ertapenem was used because its long half-life permits once-daily dosing in an outpatient setting by a peripherally inserted central catheter or a tunnelled central venous catheter (Hickman line) [15,16]. Prophylactic fluconazole was prescribed because of the high incidence of concomitant infections and current level 1 evidence [17]. Antibiotic therapy was continued for at least 6 weeks and was followed by a repeat CT assessment. If there were signs of ongoing infection clinically, biochemically or radiographically, then antibiotics were continued until resolution. The treatment algorithm in Fig. 1 outlines the approach used to supplement the existing IPN treatment guidelines.

Patients not fitting the above criteria were managed according to the 'step-up approach' with a radiologically inserted drain and subsequent minimal access retroperitoneal necrosectomy (MARPN), if necessary. Open surgery was only considered when the treating clinicians felt that intervention was time critical and that the patient would deteriorate without immediate debridement.

A prospectively maintained database of patients treated by the unit was retrospectively examined with supplementary data obtained through interrogation of patient notes and electronic hospital records. The modified Glasgow score was calculated from the initial presentation of AP and the serum C-reactive protein (CRP), white blood cell, haemoglobin and albumin were measured at diagnosis of IPN [18]. All CT scans were reviewed by a specialist abdominal, consultant radiologist and graded using the

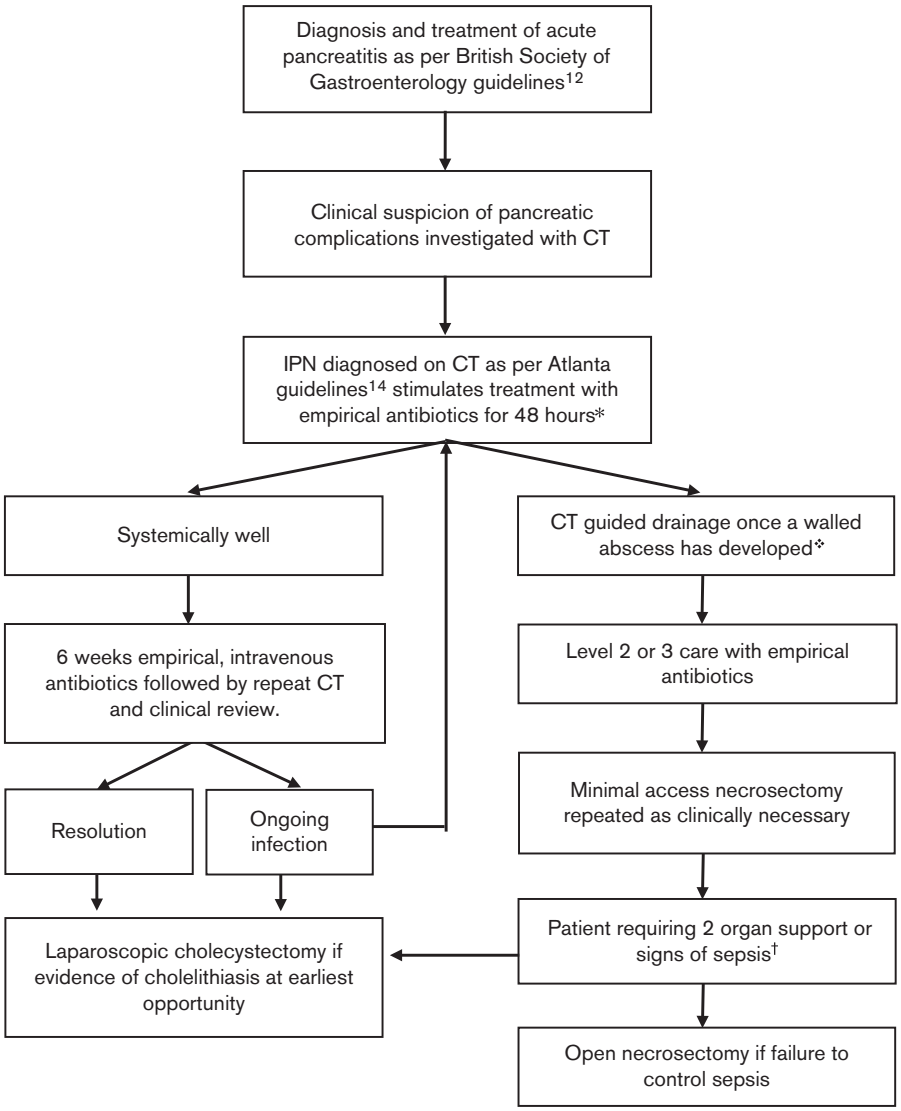

Fig. 1. Infected pancreatic necrosis (IPN) treatment algorithm. Note: Choledocholithiasis should be treated urgently with ERCP as per the BSG guidelines [12]. *Empirical antibiotics are a carbapenem such as meropenem or imipenem. †Sepsis defined as 'life-threatening organ dysfunction caused by a dysregulated host response to a new infection' [13]. ❖IAP guidelines recommend this is at least 4 weeks after the presentation of acute pancreatitis. BSG, British Society of Gastroenterology; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography; IAP, International Association of Pancreatology.

modified CT severity index (CTSI) [19]. Follow-up was detailed as the last outpatient visit and if this was not recent, then, after local ethics approval, a postal questionnaire was sent to patients treated with antibiotics only.

Comparisons between patient cohorts were made using statistical tests appropriate for nonparametric data; the Mann–Whitney *U*-test was used for continuous variables and the Pearson χ^2-test for categorical variables. All statistical analysis was conducted using SPSS, version 23 (IBM Corp., Armonk, New York, USA).

Results

Between June 2009 and January 2017, 114 patients with infected, peri-pancreatic complications of AP were managed by our tertiary pancreatic unit; 42 of whom had been transferred from a peripheral hospital. An open surgical approach was undertaken directly in five patients. Forty-four patients underwent one or more MARPN procedures; 65 patients were managed with a percutaneous drain. Four cases of infected pseudocysts were managed in a conservative way, but have been excluded from this analysis.

In total, 33 patients (20 males and 13 females) were diagnosed with IPN on radiological features. Of these, 13 were treated with antibiotics only, on an intention to treat, and did not require a fine-needle aspiration (FNA), percutaneous drain or surgical intervention. Twenty patients underwent a percutaneous, radiologically placed drain and went on to have one or more MARPN procedures. No patients with IPN were treated with percutaneous drainage alone.

Antibiotics-only group

IPN was diagnosed on readmission to hospital after the initial episode of AP in 10 patients. A single patient was diagnosed with IPN as an outpatient and completed his treatment entirely in the outpatient setting. Three patients remained in their peripheral hospital with input from the pancreatic team. A short stay on a high dependency unit was required by two of 13 patients for fluid management only. All, but two, patients completed the course of antibiotics as an outpatient.

Antibiotic use before diagnosis with IPN was variable, but most frequently meropenem (23%) or piperacillin/tazobactam (23%) was used. Following diagnosis, 12 patients received long course ertapenem treatment and one patient, who had developed iatrogenic pancreatitis post-endoscopic retrograde pancreatography, received 3 weeks of intravenous meropenem as an inpatient and was discharged after resolution of CT findings. The aetiology of the remaining cases of IPN treated conservatively was gallstones in nine patients and idiopathic in three patients. There was no disease-specific mortality; however, one elderly patient died from metastatic cholangiocarcinoma over 2 years after developing IPN.

A single patient suffered a mild episode of pancreatitis 23 months after IPN and another developed a small liver abscess (<2 cm) 38 months after diagnosis of IPN. Both patients were found to have common bile duct strictures and required endoscopic biliary stenting. Follow-up CT scanning within the rest of this group showed no remaining collections in nine patients, and small residual collections in three patients (these were not reimaged again). Full pancreatic insufficiency developed in one patient.

MARPN group

All 20 patients with IPN diagnosed on CT criteria and treated by MARPN were admitted to the ICU in our hospital for at least two organ support. Half of the patients were transferred from a peripheral hospital to our unit. Within this intervention group, 12 patients received intravenous meropenem, two imipenem, four piperacillin/tazobactam, one vancomycin and one gentamicin. The antibiotic regimens were based on the microscopy, culture and sensitivity results from pancreatic tissue and fluid samples. All of these patients received an intravenous antifungal medication (fluconazole; Pfizer, Kent, UK).

The predominant cause of AP in the intervention group was cholelithiasis; however, one patient was too unwell to undergo any significant investigation and subsequently died. The remaining cases were caused by dyslipidaemia in one patient and idiopathic in three patients. There were nine mortalities (median survival: 2.5 months, interquartile range: 1–4) and none of the surviving patients suffered further attacks of AP. At follow-up, pancreatic enzyme supplementation was needed by seven of 11 patients with four patients also needing insulin therapy. A further two patients developed non-insulin-dependent diabetes.

Group comparisons

Patients and disease characteristics are compared in Table 1. The predicted severity of AP, using the modified Glasgow score, was less in the antibiotic-only group ($P<0.001$), with CTSI scores indicating less severe features on CT ($P=0.014$). Patients who underwent MARPN had a lower serum haemoglobin and albumin levels than those who were treated by antibiotics alone ($P=0.030$ and 0.001, respectively) and a higher CRP ($P=0.027$).

Discussion

The mortality from AP has progressively fallen over recent years and can be attributed to both improvements in critical care and a decreased enthusiasm among surgeons to

Table 1. Comparison of patients with infected pancreatic necrosis treated by antibiotics only or by minimal access retroperitoneal pancreatic necrosectomy

	Antibiotics only [median (IQR)]	MARPN [median (IQR)]	*P* value[a]
Age (years)	71 (63–77)	65 (58–75)	0.128
Glasgow score	2 (1–3)	4 (3–5)	**<0.001**
Time to IPN on CT (days)	37 (19–62)	22 (8–50)	0.158
CTSI score/10	7 (6–8)	10 (8–10)	**0.014**
Hb (g/l)	109 (91–116)	90 (82–102)	**0.030**
WBC	12.8 (8.7–13.3)	13.6 (8.3–18.8)	0.221
Albumin	30 (25–32)	19 (16–23)	**0.001**
CRP	118 (68–297)	264 (191–329)	**0.027**

Bold values are less than 0.05 and considered statistically significant.
CRP, C-reactive protein; CT, computed tomography; CTSI, CT severity index; Hb, haemoglobin; IPN, infected pancreatic necrosis; IQR, interquartile range; MARPN, minimal access retroperitoneal pancreatic necrosectomy; WBC, white blood cell.
[a]Mann–Whitney *U*-test.

Table 2. Summary of published studies that have treated infected pancreatic necrosis with antibiotics only

References	*n*	Patient selection	Ranson score[a]	Antibiotics used (route)	Duration of antibiotic[a] (range) (days)	Follow-up
Amico *et al.* [8]	1	Refused surgical intervention	Not stated	Ciprofloxacin + metronidazole (i.v.)	13[a]	Complete resolution on USS at 4 months
Lee *et al.* [26]	8	Unspecified clinical assessment	3.8 (including patients treated with surgery)	Combinations of metronidazole, cefotaxime, ciprofloxacin, imipenem, amikacin, vancomycin, clindamycin, aztreonam (NS)	55.9[b]	Not mentioned within the conservative treatment group specifically
This study	13	Clinical condition and absence of organ failure	4 (1–6) APACHE II (14)	Ertapenem/meropenem/ciprofloxacin (i.v.) + fluconazole (O)	70[a] (21–112)	Complete resolution in eight cases, three residual abscesses without gas, two residual abscesses with gas
Ramesh *et al.* [9]	2	Unspecified clinical assessment	6.5 (6–7)	Third generation cephalosporin + metronidazole (i.v.)	43[a]	Complete resolution on CT at 3.5 and 4 months
Rasslan *et al.* [27]	6	Clinical condition and absence of organ failure	APACHE II 5 (0–10)	Ciprofloxacin and metronidazole, imipenem	>21	Two patients had recurrent IPN before cholecystectomy. No mortality
Sivasankar *et al.* [28]	6	Refused surgical intervention	Not stated	Ciprofloxacin, imipenem, metronidazole ± cefotaxime (NS)	40[a] (20–42)	Complete resolution on CT ranging from 1.5 to 3 months
Van Santvoort *et al.* [4]	11	Clinical condition and absence of organ failure	Not stated	Not stated	Not stated	Not stated, but 0% mortality

APACHE, Acute Physiology and Chronic Health Evaluation; CT, computed tomography; IPN, infected pancreatic necrosis; IQR, interquartile range; i.v., intravenous; NS, not specified; O, orally; USS, ultrasound scan.
[a]Median.
[b]Mean.

perform open surgery [7,20,21]. Operating within the first 14 days of the onset of AP had been associated with a mortality of up to 75% [22]. IPN continues to represent a deadly complication requiring prolonged treatments. Although the original step-up approach does not mention newer techniques such as endoscopic transgastric necrosectomy, it continues to provide a framework for treating IPN conservatively. Those that manage patients with severe AP will be aware of the broad spectrum of disease and may be familiar with patients who develop complications, but remain clinically well. Many guidelines elude to this cohort of patients, but our experiences here confirm that a structured, conservative approach is safe and effective in patients of this nature.

Repeated clinical review is fundamental in patients with AP, especially when using conservative treatments. The patients we treated with antibiotics were physiologically stable and none needed to cross into the intervention group. This reinforces our selection criteria and supports the findings by Larvin [23] who observed that an assessment by an experienced clinician can be as good at predicting outcomes as a multifactorial scoring system.

High-resolution CT scans are an invaluable tool in identifying complications of AP and correlate well with severity [19]. The results of our cohort comparisons show that even within the diagnosis of IPN on CT there is a spectrum of severity, and those with a lower CTSI score respond to conservative treatment. This group of patients also exhibits less abnormal serum haemoglobin and albumin levels. The intravascular volume depletion caused by the systemic effects of AP can require copious fluid resuscitation and, thus, these diluted blood constituents likely reflect the overall condition of the patient [24]. As for the CRP, it has long been known to correlate with the development of pancreatic complications and this study has shown that it may not only have a role in identification, but also in stratification of IPN [25].

A distinguishing feature of these cases could be in their delayed presentation. The work carried out by Besselink *et al.* [22] observed that IPN had a median time of onset 26 days from admission with AP. In comparison, the time to IPN in our population was 37 and 22 in the antibiotic-only and MARPN groups, respectively. Whether this is a delay in the diagnosis or a delay in the onset on the condition is not known, but again hints at a less aggressive disease process. This is evidenced further as 10 of 13 patients were discharged after their initial episode of pancreatitis; only two patients needed high dependency level 2 care and one patient had IPN diagnosed as an outpatient.

A search of the literature finds many instances of IPN being treated conservatively, but relatively few without even an FNA. The 34 published cases are summarized in Table 2, and exhibit a rather ad-hoc treatment methodology [4,8,9,26,28]. A number of patients simply had a serendipitous response to antibiotics after refusing surgical interventions [8,28]. There is a marked heterogeneity between the studies because of the various antibiotics and their durations. Comparisons can also be difficult because much of the terminology surrounding AP has developed over recent years and as such the definitions and classifications of AP, and the radiological findings, have changed. Nonetheless, these cases should be regarded as an evidence that there are patients who could have undergone unnecessary interventions if the existing guidelines were followed to the latter.

Despite being the largest case series of IPN, managed entirely without drainage, this study remains small and is largely retrospective in its design. As the tertiary centre, we are reliant upon referrals to identify many of the cases and this may have introduced a selection bias. A more significant area of controversy may lie in our diagnosis of IPN. The presence of peri-pancreatic, extra-luminal gas on CT is regarded as pathognomonic by many, but we recognize that the gold standard for diagnosing infection would be an FNA with microbial analysis [5,29]. The

authors' views are that this procedure, for purely diagnostic reasons, is unnecessary as it would not alter the management of the patient. The peri-pancreatic gas could indeed have another source, namely an enteric fistula. CT scans used in this series were thoroughly scrutinized and we are confident that there was no evidence of this. We postulate that the complete resolution witnessed in our patients may have occurred through the fistulation and drainage of purulent material through the pancreatic duct.

Conclusion

This study represents the largest case series of IPN successfully treated using a conservative approach with long-term antibiotics. This management technique should be used to supplement existing treatment guidelines in the management of IPN and does not go against the drainage and 'step-up' approach in an unwell, septic patient. Further work is needed to define the patient cohort that benefit from antibiotic therapy alone and allow the reliable identification of these patients.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Fitz R. Acute pancreatitis, a consideration of hemorrhage, hemorrhagic, suppurative, and gangrenous pancreatitis, and of disseminated fat necrosis. *Boston Med Surg J* 1889; 70:181–235.
2 Widdison AL, Karanjia ND. Pancreatic infection complicating acute pancreatitis. *Br J Surg* 1993; 80:148–154.
3 Petrov MS, Shanbhag S, Chakraborty M, Phillips AR, Windsor JA. Organ failure and infection of pancreatic necrosis as determinants of mortality in patients with acute pancreatitis. *Gastroenterology* 2010; 139:813–2010.
4 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; 141:1254–6310.
5 Working Group IAPAPAAPG. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; 13:e1–1510.
6 Kokosis G, Perez A, Pappas TN. Surgical management of necrotizing pancreatitis: an overview. *World J Gastroenterol* 2014; 20:16106–16112.
7 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.
8 Amico EC, Canedo LF, Machado CC, Faria SG, Vivas DV. Conservative treatment of pancreatic necrosis with suggestive signs of infection. *Clinics (Sao Paulo)* 2005; 60:429–432.
9 Ramesh H, Prakash K, Lekha V, Jacob G, Venugopal A. Are some cases of infected pancreatic necrosis treatable without intervention? *Dig Surg* 2003; 20:296–299.
10 Welsh Government. *Mid-year population estimates (2009 onwards), by Welsh health boards, for single year of age and gender*. Cardiff, UK: Welsh Government; 2016.
11 NHS Wales Information Services. PEDW 2015/16 Primary Diagnosis Data Tables; 2017. Available at: *http://www.infoandstats.wales.nhs.uk/page.cfm?orgid=869&pid=41010&subjectlist=External+Causes+by+LHB+Provider&patientcoverlist=0&period=2015&keyword=&action=Search*. [Accessed 14 February 2018].
12 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 G. I. Surgeons of Great Britain and Ireland. UK guidelines for the management of acute pancreatitis. *Gut* 2005; 54 (Suppl 3):iii1–iii9.
13 Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, *et al*. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; 315:801–810.
14 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.
15 Buchler M, Malfertheiner P, Friess H, Isenmann R, Vanek E, Grimm H, *et al*. Human pancreatic tissue concentration of bactericidal antibiotics. *Gastroenterology* 1992; 103:1902–1908.
16 Zhanel GG, Wiebe R, Dilay L, Thomson K, Rubinstein E, Hoban DJ, *et al*. Comparative review of the carbapenems. *Drugs* 2007; 67:1027–1052.
17 Cortegiani A, Russotto V, Maggiore A, Attanasio M, Naro AR, Raineri SM, *et al*. Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients. *Cochrane Database Syst Rev* 2016; 2016:CD00492010.
18 Blamey SL, Imrie CW, O'Neill J, Gilmour WH, Carter DC. Prognostic factors in acute pancreatitis. *Gut* 1984; 25:1340–1346.
19 Mortele KJ, Wiesner W, Intriere L, Shankar S, Zou KH, Kalantari BN, *et al*. A modified CT severity index for evaluating acute pancreatitis: improved correlation with patient outcome. *Am J Roentgenol* 2004; 183:1261–1510.
20 Pavlidis P, Crichton S, Lemmich Smith J, Morrison D, Atkinson S, Wyncoll D, *et al*. Improved outcome of severe acute pancreatitis in the intensive care unit. *Crit Care Res Pract* 2013; 2013:897107.
21 Wormer BA, Swan RZ, Williams KB, Bradley JF 3rd, Walters AL, Augenstein VA, *et al*. Outcomes of pancreatic debridement in acute pancreatitis: analysis of the nationwide inpatient sample from 1998 to 2010. *Am J Surg* 2014; 208:350–6210.
22 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.
23 Larvin M. Assessment of severity and prognosis in acute pancreatitis. *Eur J Gastroenterol Hepatol* 1997; 9:122–130.
24 Garcia M, Calvo JJ. Cardiocirculatory pathophysiological mechanisms in severe acute pancreatitis. *World J Gastrointest Pharmacol Ther* 2010; 1:9–14.
25 Mayer AD, McMahon MJ, Bowen M, Cooper EH. C reactive protein: an aid to assessment and monitoring of acute pancreatitis. *J Clin Pathol* 1984; 37:207–211.
26 Lee JK, Kwak KK, Park JK, Yoon WJ, Lee SH, Ryu JK, *et al*. The efficacy of nonsurgical treatment of infected pancreatic necrosis. *Pancreas* 2007; 34:399–404.
27 Rasslan R, Rocha MC, Bitran A, de Souza Rocha M, de Oliveira, Bernini C, *et al*. Pancreatic necrosis and gas in the retroperitoneum: treatment with antibiotics alone. *Clinics (Sao Paulo)* 2017; 72:87–94.
28 Sivasankar A, Kannan DG, Ravichandran P, Jeswanth S, Balachandar TG, Surendran R. Outcome of severe acute pancreatitis: is there a role for conservative management of infected pancreatic necrosis? *Hepatobiliary Pancreat Dis Int* 2006; 5:599–604.
29 Isaji S, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, *et al*. JPN Guidelines for the management of acute pancreatitis: surgical management. *J Hepatobiliary Pancreat Surg* 2006; 13:48–55.