

Mistakes in the management of acute pancreatitis and how to avoid them

Georg Beyer, Peter Simon, Julia Mayerle and Markus M. Lerch

Acute pancreatitis is a common inflammatory disorder of the pancreas and its incidence is increasing among hospitalized patients worldwide. In 2009, it was the most frequent diagnosis in patients discharged from GI services in the US and the fifth leading cause of in-hospital mortality.¹ Because of this high disease burden, acute pancreatitis is also a substantial contributor to healthcare spending, accounting for an estimated annual spend of US\$4–7 million per million inhabitants in western countries.^{2,3} The main symptoms include severe upper abdominal pain (often sudden onset), nausea, vomiting, bloating and the development of ileus. In many cases jaundice will also be present. The diagnosis, as agreed by international consensus, can be established by fulfilling two of the following three criteria: upper abdominal pain of sudden onset, elevation of either serum lipase or amylase activity to greater than three times the upper limit of normal, and imaging findings consistent with inflammation of the pancreas.^{4–6}



Image courtesy of G. Beyer et al

By far the most common risk factors for the development of acute pancreatitis are excessive alcohol consumption and gallstone disease. Several mutations have been identified that, in combination with nongenetic factors or alone, can lead to pancreatitis. Certain drugs are known to be associated with the development of pancreatitis and smoking might also increase the probability of it developing. 80–85% of patients diagnosed with the disease will have mild disease and make an uneventful recovery with little more than adequate fluid therapy and analgesia needed to support them. The remaining patients, however, will suffer from moderately severe to severe acute pancreatitis, with the development of pancreatic necrosis, severe sepsis or abdominal compartment syndrome. These patients are at immediate danger of multiorgan failure and death and require multidisciplinary intensive care, organ support and often pancreatic interventions conducted by experienced investigators. Since it is difficult to predict outcomes and complications develop during the disease course, treatment in specialized centres that have a high case load is recommended.^{4–6}

Here, we discuss critical decision-making points and pitfalls frequently occurring when managing patients with acute pancreatitis. The discussion is based on the medical literature and many years of clinical experience.

Mistake 1 Failing to adequately assess fluid status

Early and adequate fluid resuscitation is a cornerstone in the management of acute pancreatitis and perhaps the most critical part of active treatment within the first 48 hours from the point of diagnosis. Although the number of trials is limited, it is now widely accepted that fluid sequestration due to third spacing is a common early event in acute pancreatitis, and is associated with pancreatic necrosis and organ failure if not treated immediately.^{7–9} Several parameters that have been found to predict a more severe course of acute pancreatitis early in its course, such as

a high haematocrit, rising BUN (blood urea nitrogen) or creatinine levels raised above the age-adjusted upper limit of normal or significantly increased from previous levels, are directly linked to intravascular fluid state and organ perfusion.^{10,11} Therefore, aggressive fluid resuscitation has been promoted, with administration of large amounts of crystalloid and/or colloid solutions within the first 2 days from admission, often exceeding 6l or more.^{12,13}

We have now learned from a number of trials that overly aggressive administration is not necessarily beneficial for patients and could even be harmful. In two consecutively

published randomized trials from China, overly rapid fluid expansion with hourly rates exceeding 10ml/kg body weight or haemodilution to a haematocrit lower than 35% within 48 hours were shown to put patients at risk of needing mechanical ventilation, sepsis and death.^{14,15} Additionally, a meta-analysis of intensive care patients undergoing fluid resuscitation for various reasons (not only pancreatitis) showed that fluid amounts exceeding 7.5l increased the risk of intra-abdominal hypertension and abdominal compartment syndrome,¹⁶ one of the most lethal complications of acute pancreatitis.¹⁷

Different approaches taken to fluid resuscitation, by aiming for specific goals in reaching physiologic and laboratory parameters deduced from the prognostic studies (goal-directed fluid resuscitation), have so far failed to improve patient outcomes in studies of both pancreatitis and non-pancreatitis patients.^{15,18,19}

In light of these contradictory data, current guidelines suggest adopting a pragmatic approach based on the available studies and expert opinions with moderately aggressive fluid resuscitation.⁵ In view of the lack of further evidence, patients should receive crystalloid fluids, rather than colloids, at a rate of 5–10ml/kg of body weight to reach the following goals:

- Heart rate <120 bpm under adequate analgesic therapy
- Mean arterial pressure 65–85mmHg with urine output >0.5ml/kg body weight per hour
- Haematocrit 35–44%

Alternatively, novel techniques such as thermodilution and stroke volume variation, can determine the required amount of fluid replacement. At the same time, physicians

© UEG 2016 Beyer et al.

Cite this article as: Beyer G, et al. Mistakes in the management of acute pancreatitis and how to avoid them. *UEG Education* 2016; 16: 27–30.

Georg Beyer, Peter Simon, Julia Mayerle and Markus M. Lerch are at the Department of Medicine A, University Medicine Greifswald, Germany.

Correspondence to: georg.beyer@uni-greifswald.de
Published online: 24 August 2016

need to look out for fluid overload, such as increasing oxygen requirements or respiratory rate. Patients with pre-existing heart failure, cardiac valve disease or renal disease are at increased risk due to a lower ability to handle large amounts of fluid.^{6,20} Intra-abdominal pressure should be monitored intermittently using intravesical catheter systems in patients who have a predicted severe disease course or unexplained deterioration.

Mistake 2 Delaying ERCP in patients with acute pancreatitis and cholangitis

Gallstone disease is a leading cause of acute pancreatitis. Patients often present with a history of cholelithiasis and symptoms of cholestasis, reporting right upper quadrant pain as the initial symptom. However, acute pancreatitis will often be accompanied by derangement of liver function test results and jaundice, even without pre-existing biliary disease. Inflammation in the head of the pancreas and peripancreatic, papillary or duodenal oedema can lead to biliary obstruction even without choledocholithiasis.

While diagnostic endoscopic retrograde cholangiopancreatography (ERCP) has mostly lost its place in the management of pancreatic disease, and endoscopic interventions in patients with acute pancreatitis need to be delayed as much as possible (as discussed below), the need for an early ERCP with sphincterotomy (within 24h) for stone removal and/or bile-duct stenting can be a critical decision in the early management of acute pancreatitis. Guidelines recommend ERCP if there is evidence of concurrent common bile duct obstruction or signs of cholangitis.^{4,5} If the course of biliary pancreatitis is predicted to be mild and evidence for obstruction of the common bile duct is missing, patients might be managed without ERCP as the potential benefit does not outweigh the risk of additional adverse events caused by the intervention.²¹ In most cases of biliary pancreatitis, the disease-triggering stone that has led to temporary pancreatic duct obstruction and thus induced pancreatitis has already passed into the duodenum and no longer requires interventional removal.

In patients who have no cholangitis but unclear derangement of liver function test

results and/or a history of gallstones, MRCP or EUS can help to avoid ERCP by ruling out the presence of obstructing stones. EUS is more sensitive due to its high resolution, but MRCP might be more broadly available and is less operator dependent.

If there are strong indications for cholangitis at the point of diagnosis of acute pancreatitis, ERCP with sphincterotomy should be performed without delay, even if there is no proof that there are common bile duct stones. Cholangitis can rapidly progress to cholangiosepsis, putting patients at great risk of organ failure and death. Establishment of biliary drainage is therefore a priority in these patients. The optimal timing for ERCP in a patient with stones obstructing the common bile duct, but without cholangitis is unknown.²² A prospective observational study indicated that patients who have predicted severe disease would benefit from urgent ERCP.²³ A randomized multicentre trial to investigate the role of early ERCP with sphincterotomy in patients who have predicted severe biliary pancreatitis, but no cholangitis, is currently being conducted in the Netherlands.²⁴ At present, the evidence points to early ERCP conferring a much greater benefit on the course of cholangitis than for the actual pancreatitis induced by the impacted gallstone.

Mistake 3 Delaying cholecystectomy in patients with biliary pancreatitis

Patients with biliary pancreatitis are at high risk of recurrence if the source of the migrating gallstones, the gallbladder, is not removed. Therefore, cholecystectomy is indicated in all patients with a biliary aetiology of pancreatitis. Once again, the timing of the intervention depends on the course of the disease. In patients who have mild biliary pancreatitis, cholecystectomy can safely be performed during the index hospital admission, as recently demonstrated.²⁵ Alternatively, a sphincterotomy will decrease the risk of recurrent pancreatitis without eliminating it. However, ERCP is rarely performed in patients with mild disease, as described above. Prophylactic sphincterotomy should be considered in patients who are unfit for surgery due to comorbidities.²⁶ In those with severe biliary pancreatitis, cholecystectomy should be delayed until resolution of pancreatic collections or formation of a walled-off necrosis (WON), after which it can be safely performed. Delaying removal of the gallbladder beyond 6 weeks from admission increases the risk of recurrent biliary events including pancreatitis and should be avoided (Figure 1).

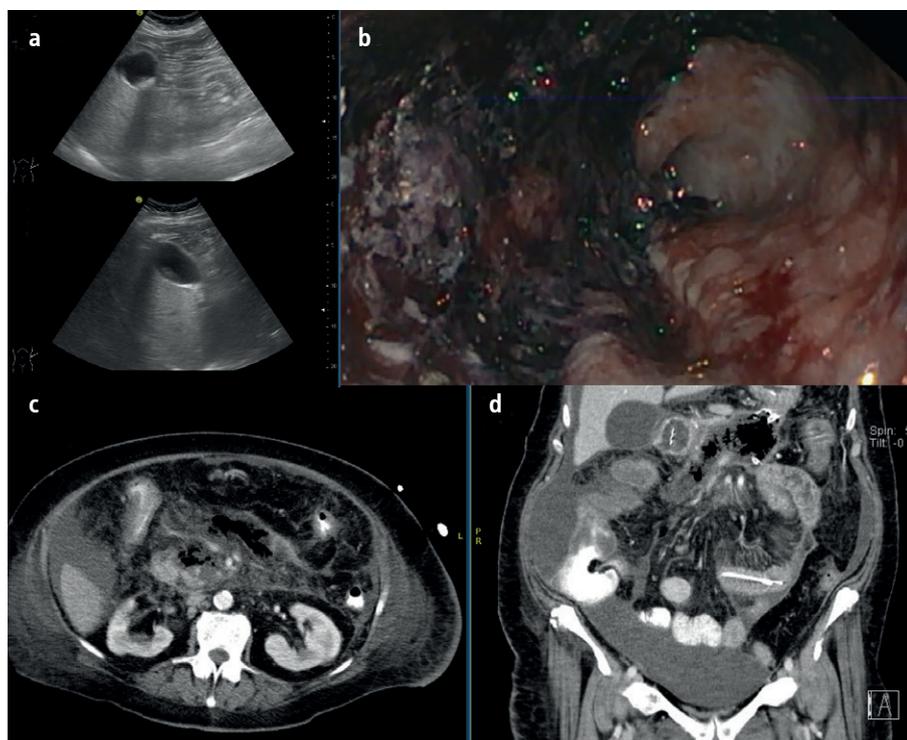


Figure 1 | A 74-year-old woman with a history of hypertension, diabetes and kidney stones first presented to the GI service in May 2015 with a mild acute pancreatitis due to previously undetected gall stones (a). ERCP was not indicated as there was no sign of persistent cholestasis or cholangitis. Cholecystectomy was not performed during the index stay, but was strongly recommended at discharge. The patient missed her appointment for cholecystectomy and was lost to follow-up. In September 2015 the patient was readmitted with biliary pancreatitis and developed a severe course with organ failure, infected pancreatic and retroperitoneal necrotic collections and a disconnected duct (c, d) which were managed with percutaneous drains, a transgastric metal stent as well as transpapillary stenting. She underwent numerous endoscopic necrosectomies (b) and had to be readmitted to the hospital multiple times. Cholecystectomy could finally be performed in May 2016, one year after the initial event.

Mistake 4 Early surgical or endoscopic intervention for acute necrotizing pancreatitis

Over the course of the past 10 years the strategy for interventions in acute necrotizing pancreatitis has changed drastically. For a long time, treatment of pancreatic necrosis included open surgical necrosectomy, which was associated with high complication rates and significant mortality even at high-volume centres. Several trials led to a paradigm shift towards two main principles in the management of acute pancreatic necrosis. First, interventions should be delayed to at least 4 weeks after the onset of acute pancreatitis whenever possible. Second, a step-up approach should be followed, starting with endoscopic or minimal invasive percutaneous drainage procedures.

Indications for interventions are proof that there is a necrotic collection on imaging that shows features of infection or high suspicion for infection with persistent signs of sepsis. Other reasons for intervention include being persistently unwell, disconnected duct syndrome, gastric outlet obstruction or pancreatic fistulas. Clinical experience shows that intervention to treat an infected pancreatic necrosis before it has sufficiently walled off (i.e. before the WON period) is associated with a higher risk of technical failures and adverse events due to rupture of the collection, dislocation of catheters or bleeding. In addition, in some patients even infected necrotic collections can be managed conservatively with intravenous antibiotics and supportive therapy only,²⁷ although this subgroup of patients has not been well characterized yet. In a substantial percentage of patients who have infected necrosis drainage by means of endoscopic stent placement (double pigtail stents or self-expanding wall stents) or percutaneous retroperitoneal tubes will lead to resolution of the collection without the need for subsequent surgery. A drainage procedure should, therefore, be considered first.

If drainage and irrigation alone does not lead to improvement, minimal invasive necrosectomy either endoscopically or via the percutaneous access should be considered. A randomized trial has demonstrated superiority of endoscopic necrosectomy over surgical necrosectomy.²⁸ Open surgery for debridement, drainage of a collection or pancreatic resection is reserved for patients in whom the previously mentioned methods have failed to improve the situation.^{4,5}

Mistake 5 Administering prophylactic antibiotics

On the basis of the two most recent meta-analyses, current Western guidelines do not

support the routine use of prophylactic antibiotics in patients who have acute pancreatitis. It is, therefore, recommended that systemic antibiotics be started only if an infection, pancreatic or not, is proven or very likely.^{4,5} In daily practice, however, it is acknowledged that risk stratification can be somewhat difficult, due to the fact that patients with acute pancreatitis often fulfill the criteria for a systemic inflammatory response syndrome (SIRS) or quick sequential organ failure assessment score (qSOFA) at the time of presentation, especially those who have predicted severe disease. This difficulty can be caused by either sterile pancreatic inflammation or sepsis with pancreatitis.

By contrast, the most recently published Japanese guideline, which is based on a meta-analysis of six RCTs, states that early (48–72hrs) prophylactic administration of antibiotics in patients with severe and necrotizing pancreatitis might reduce mortality and the rate of infected necrosis.^{6,29} These findings therefore leave room for further discussion and more prospective trials on the role of prophylactic antibiotics in predicted severe disease are needed. Currently, administration of prophylactic antibiotics is not recommended, but the threshold for administration in unwell patients should be set low.

Mistake 6 Recommending unnecessary bowel rest

There is currently little dispute that patients who have acute pancreatitis do not benefit from being starved. The old concept that nonstimulation of the pancreas by resting the alimentary tract will support pancreatic healing is obsolete. By contrast, it is now believed that enteral feeding prevents mucosal atrophy of the gut and thus prevents bacterial translocation and intra-abdominal infection. More than providing only nutrition, feeding serves an anti-infectious purpose in the early phase of acute pancreatitis.⁶

The timing and method of feeding depend on the course of disease. In general patients who have mild disease can resume their normal oral diet as soon as their symptoms (pain and nausea) allow and inflammatory markers are on the decline. Prokinetics might help to increase tolerance towards an oral diet. Only rarely is a feeding tube required in cases of mild pancreatitis. In patients with severe disease nutritional support is often needed, but the optimal time point for initiation of feeding is still unknown. In a Dutch multicentre randomized trial, patients with a predicted severe disease did not benefit from nasoenteric tube feeding

started within 24h compared with feeding started after 72h.³⁰

Taken together, patients with pancreatitis do not benefit from bowel rest, but timely limited underfeeding seems to not cause harm.^{5,6} Total parenteral nutrition should be avoided to prevent infectious complications.⁴

Mistake 7 Performing routine cross-sectional imaging on admission

In the vast majority of patients, the diagnosis of acute pancreatitis can be established without the need for proof by cross-sectional imaging. Because of this, and for several other reasons, current guidelines do not recommend routinely performing a CT scan in the first two to three days after the onset of symptoms.

First, and most importantly, an early scan might not be of therapeutic consequence because it does not trigger any treatment decisions at this point in time. The extent of the disease, especially necrosis, might not be fully visible before several days into the disease course. Second, there is no evidence that an early scan helps to predict the severity of disease. Morphologic scoring systems are not superior to clinical evaluation. Third, fluid sequestration is a major problem during the early phase of pancreatitis and contrast enhancement increases the risk of additional kidney damage occurring during this vulnerable phase.

Exceptional indications for an early cross-sectional scan include cases of diagnostic uncertainty, suspicion for abdominal compartment syndrome or vascular complications including haemorrhage or bowel ischaemia.^{4–6} T2-weighted MRI without gadolinium is advisable if kidney damage is present. For evaluation of cholestasis, CT is not superior to transabdominal ultrasound and laboratory studies, but the use of EUS or MRCP should be considered if the presence of obstructing stones in patients with severe disease cannot be ruled out by transabdominal ultrasound.^{5,6}

Conflicts of interest: The authors declare there are no conflicts of interest.

References

1. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012; 143: 1179–1187.e1–3.
2. Fagenholz PJ, Fernández-del Castillo C, Harris NS, et al. Direct medical costs of acute pancreatitis hospitalizations in the United States. *Pancreas* 2007; 35: 302–307.
3. Andersson B, Appelgren B, Sjödin V, et al. Acute pancreatitis—costs for healthcare and loss of production. *Scand J Gastroenterol* 2013; 48: 1459–1465.
4. Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; 108: 1400–1415.

5. Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; 13: e1–15.
6. Yokoe M, Takada T, Mayumi T, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. *J Hepato-Biliary-Pancreat Sci* 2015; 22: 405–432.
7. de-Madaria E, Banks PA, Moya-Hoyo N, et al. Early factors associated with fluid sequestration and outcomes of patients with acute pancreatitis. *Clin Gastroenterol Hepatol* 2014; 12: 997–1002.
8. Wall I, Badalov N, Baradaran R, et al. Decreased mortality in acute pancreatitis related to early aggressive hydration. *Pancreas* 2011; 40: 547–550.
9. Brown A, Baillargeon J-D, Hughes MD, et al. Can fluid resuscitation prevent pancreatic necrosis in severe acute pancreatitis? *Pancreatology* 2002; 2: 104–107.
10. Wu BU, Johannes RS, Sun X, et al. Early changes in blood urea nitrogen predict mortality in acute pancreatitis. *Gastroenterology* 2009; 137: 129–135.
11. Koutroumpakis E, Wu BU, Bakker OJ, et al. Admission hematocrit and rise in blood urea nitrogen at 24 h outperform other laboratory markers in predicting persistent organ failure and pancreatic necrosis in acute pancreatitis: a post hoc analysis of three large prospective databases. *Am J Gastroenterol* 2015; 110: 1707–1716.
12. Gardner TB, Vege SS, Chari ST, et al. Faster rate of initial fluid resuscitation in severe acute pancreatitis diminishes in-hospital mortality. *Pancreatology* 2009; 9: 770–776.
13. Haydock MD, Mittal A, Wilms HR, et al. Fluid therapy in acute pancreatitis: anybody's guess. *Ann Surg* 2013; 257: 182–188.
14. Mao E-Q, Tang Y-Q, Fei J, et al. Fluid therapy for severe acute pancreatitis in acute response stage. *Chin Med J (Engl)* 2009; 122: 169–173.
15. Mao E-Q, Fei J, Peng Y-B, et al. Rapid hemodilution is associated with increased sepsis and mortality among patients with severe acute pancreatitis. *Chin Med J (Engl)* 2010; 123: 1639–1644.
16. Holodinsky JK, Roberts DJ, Ball CG, et al. Risk factors for intra-abdominal hypertension and abdominal compartment syndrome among adult intensive care unit patients: a systematic review and meta-analysis. *Crit Care* 2013; 17: R249.
17. Trikudanathan G and Vege SS. Current concepts of the role of abdominal compartment syndrome in acute pancreatitis—an opportunity or merely an epiphenomenon. *Pancreatology* 2014; 14: 238–243.
18. Wu BU, Hwang JQ, Gardner TH, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. *Clin Gastroenterol Hepatol* 2011; 9: 710–717.e1.
19. ARISE Investigators, ANZICS Clinical Trials Group. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med* 2014; 371: 1496–1506.
20. DiMaggio MJ. Clinical update on fluid therapy and nutritional support in acute pancreatitis. *Pancreatology* 2015; 15: 583–588.
21. Fölsch UR, Nitsche R, Lütke R, et al. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. *N Engl J Med* 1997; 336: 237–242.
22. Tse F, Yuan Y. Early routine endoscopic retrograde cholangiopancreatography strategy versus early conservative management strategy in acute gallstone pancreatitis. *Cochrane Database Syst Rev* 2012; 5: CD009779.
23. van Santvoort HC, Besselink MG, de Vries AC, et al. Early endoscopic retrograde cholangiopancreatography in predicted severe acute biliary pancreatitis: a prospective multicenter study. *Ann Surg* 2009; 250: 68–75.
24. Schepers NJ, Bakker OJ, Besselink MGH, et al. Early biliary decompression versus conservative treatment in acute biliary pancreatitis (APEC trial): study protocol for a randomized controlled trial. *Trials* 2016; 17: 5.
25. da Costa DW, Bouwense SA, Schepers NJ, et al. Same-admission versus interval cholecystectomy for mild gallstone pancreatitis (PONCHO): a multicentre randomised controlled trial. *Lancet* 2015; 386: 1261–1268.
26. da Costa DW, Schepers NJ, Römkens TEH, et al. Endoscopic sphincterotomy and cholecystectomy in acute biliary pancreatitis. *Surgeon* 2016; 14: 99–108.
27. Mouli VP, Sreenivas V and Garg PK. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: a systematic review and meta-analysis. *Gastroenterology* 2013; 144: 333–340.e2.
28. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA* 2012; 307: 1053–1061.
29. Isaji S, Takada T, Mayumi T, et al. Revised Japanese guidelines for the management of acute pancreatitis 2015: revised concepts and updated points. *J Hepato-Biliary-Pancreat Sci* 2015; 22: 433–445.
30. Bakker OJ, van Brunschot S, van Santvoort HC, et al. Early versus on-demand nasoenteric tube feeding in acute pancreatitis. *N Engl J Med* 2014; 371: 1983–1993.

Your acute pancreatitis briefing

UEG Week sessions

- 'Acute pancreatitis: A clinical challenge' at UEG Week 2015 [<https://www.ueg.eu/education/session-files/?session=1359&conference=109>].
- 'Acute pancreatitis: Therapeutic strategies' at UEG Week 2015 [<https://www.ueg.eu/education/session-files/?session=1352&conference=109>].
- 'Acute pancreatitis in annual review' presentation in the 'Pancreas: What's new in 2015?' session at UEG Week 2015 [<https://www.ueg.eu/education/session-files/?session=1448&conference=109>].
- 'The complex pancreatic case' at UEG Week 2015 [<https://www.ueg.eu/education/session-files/?session=1427&conference=109>].
- 'Update on the management of acute pancreatitis' at UEG Week 2014 [<https://www.ueg.eu/education/session-files/?session=1190&conference=76>].
- 'Acute pancreatitis: The most common reason for hospital admission in GI disease. Do we know enough?' at UEG Week 2013 [<https://www.ueg.eu/education/session-files/?session=602&conference=48>].

Society conferences

- 'Session 1—Acute pancreatitis' session at EFISDS & EPC Postgraduate course 2015 [<https://www.ueg.eu/education/session-files/?session=1484&conference=135>].
- 'Surgery in acute pancreatitis—Still a role and when?' presentation at EDS Postgraduate Course, 2015

[<https://www.ueg.eu/education/document/surgery-in-acute-pancreatitis-still-a-role-and-when/111521/>].

- 'Session III: Mechanisms of acute pancreatitis—Current concepts of therapy' at European Pancreatic Club 2013 [<https://www.ueg.eu/education/session-files/?session=1027&conference=42>].

Standards and Guidelines

- Tenner S, Baillie J, DeWitt J, et al. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; 108: 1400–1415 [<http://www.nature.com/ajg/journal/v108/n9/full/ajg2013218a.html>].
- Working Group IAP/APA Acute Pancreatitis Guidelines. IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; 13: e1–15 [[http://www.pancreatology.net/article/S1424-3903\(13\)00525-5/abstract](http://www.pancreatology.net/article/S1424-3903(13)00525-5/abstract)].
- Yokoe M, Takada T, Mayumi T, et al. Japanese guidelines for the management of acute pancreatitis: Japanese Guidelines 2015. *J Hepato-Biliary-Pancreat Sci* 2015; 22: 405–432 [<http://onlinelibrary.wiley.com/doi/10.1002/jhbp.259/abstract>].
- Isaji S, Takada T, Mayumi T, et al. Revised Japanese guidelines for the management of acute pancreatitis 2015: revised concepts and updated points. *J Hepato-Biliary-Pancreat Sci* 2015; 22: 433–445 [<http://onlinelibrary.wiley.com/doi/10.1002/jhbp.260/abstract>].