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Review Article

Early management of acute pancreatitis: A review of the best evidence

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ABSTRACT

In the 20th century early management of acute pancreatitis often included surgical intervention, despite overwhelming mortality. The emergence of high-quality evidence (randomized controlled trials and meta-analyses) over the past two decades has notably shifted the treatment paradigm towards predominantly non-surgical management early in the course of acute pancreatitis. The present evidence-based review focuses on contemporary aspects of early management (which include analgesia, fluid resuscitation, antibiotics, nutrition, and endoscopic retrograde cholangiopancreatography) with a view to providing clear and succinct guidelines on early management of patients with acute pancreatitis in 2017 and beyond.

1. Introduction

Despite more than 100 years of experience and thousands of experimental and clinical studies, the management of acute pancreatitis remains challenging. In the past the slow progress has reflected the paucity of high-level evidence and an undue emphasis on surgical management. This 20th century 'surgical odyssey' has been well described [1]. The more recent application of evidence-based medicine principles to the early non-surgical management of acute pancreatitis has yielded improved patient outcomes and is the subject of this review. While there have been numerous studies demonstrating no benefit for a range of pharmacological interventions in acute pancreatitis (including but not limited to aprotinin, atropine, calcitonin, fresh frozen plasma, glucagon, gabexate, glucocorticoids, lexipafant, non-steroidal anti-inflammatory drugs, octreotide), the focus of this article is on the best available evidence on the use of early treatments that are often considered by the modern day clinicians. A computerized literature cross-search of three databases (MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials) from January 1, 1990 to September 1, 2016 was performed. To provide the best quality evidence, the data from only randomized controlled trials (RCTs) and high-quality meta-analyses in patients with acute pancreatitis were presented, if available.

2. Pain management

Pain is the cardinal symptom of acute pancreatitis and its relief is a clinical priority. Different analgesics have been compared in patients with acute pancreatitis and the nine published RCTs are summarised in Table 1 [2–10]. These trials had different study designs, evaluated different analgesics, had small sample sizes, and only three of the trials were double-blind. From these studies, it appears that there is no credible clinical evidence to avoid the use of morphine in treating the pain associated with acute pancreatitis. There is no evidence to support the use of parenterally administered local anesthetics (Procaine) in the management of pain associated with acute pancreatitis. Patients with severe pain will require intravenous analgesia and patient-controlled analgesia should be considered. Epidural analgesia can be considered for those patients with severe and critical acute pancreatitis who require high doses of opioids for an extended period. Although it has been reported that analgesics could also be given transdermally or rectally, there are no RCTs comparing the different routes of administration of the same analgesic in patients with acute pan-

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Table 1
Randomized controlled trials of analgesics in patients with acute pancreatitis.

Study ID	Year	Setting	Intervention group	Control group	No. of patients			Allocation concealment	Reduction of pain score	Other important findings
					Intervention group	Control group				
Blamey et al. [2]	1984	UK	Buprenorphine (i.m.)	Pethidine (i.m.)	17	15		Single-blind	No difference	No difference in terms of adverse effects.
Ebbehoj et al. [3]	1985	Denmark	Indomethacin (rectal)	Placebo (rectal)	14	16		Double-blind	Significantly higher in the intervention group over the first 168 h	Number of opiate injections were significantly lower in the intervention group.
Jacobs et al. [4]	2000	Germany	Buprenorphine (i.v.)	Procaine (i.v.)	20	20		Open-label	Significantly higher in the intervention group over the first 48 h	Number of additional analgesics were significantly lower in the intervention group.
Stevens et al. [5]	2002	USA	Fentanyl (transdermal)	Placebo (transdermal)	16	16		Double-blind	Significantly higher in the intervention group between 36 and 60 h	A significantly reduced length of stay in the intervention group.
Kahl et al. [6]	2004	Germany	Pentazocine (i.v.)	Procaine (i.v.)	50	51		Open-label	Significantly higher in the intervention group over the first 72 h	Number of additional analgesics were significantly lower in the intervention group.
Peiro et al. [7]	2008	Spain	Metamizole (i.v.)	Morphine (s.c.)	8	8		Open-label	Non-significantly higher in the intervention group over the first 24 h	No difference in terms of adverse effects.
Layer et al. [8]	2011	Germany	Procaine hydrochloride (i.v)	Placebo	23	21		Double-blind	Significantly higher in the intervention group over the first 72 h	Number of additional analgesics were significantly lower in the intervention group.
Sadowski et al. [9]	2015	Switzerland	Epidural anesthesia w Bupivacaine + Fentanyl	Patient controlled anesthesia (Fentanyl i.v)	13	22		Open-label	Significantly higher in the intervention group on day 0 and 10, not on days 1 to 9	Significant improvement of pancreas perfusion in the intervention group.
			Tramadol (i.v.)	Dexketoprofen (i.v.) or Paracetamol (i.v.)	30	30	60			

creatitis. Despite evidence from RCTs being available, there remains uncertainty about the preferred analgesic and the best method of administration [11]. That is why the best current recommendation at the moment is to adhere to the most current acute pain management guidelines in the perioperative setting. But all patients with acute pancreatitis must receive some form of analgesia in the first 24 h of hospitalisation in order to not compromise patient's quality of life [12–14].

3. Fluid resuscitation

Fluid resuscitation is the intervention most likely to improve clinical outcomes [15,16]. Non-mild acute pancreatitis is associated with increased fluid sequestration, which is in turn associated with hypovolemia and higher fluid requirements [17]. Six RCTs have been conducted in this area so far, of which four have come from China. The first Chinese study compared two rates of fluid infusion, 10–15 ml kg^{-1} h^{-1} versus 5–10 ml kg^{-1} h^{-1}, in patients with severe acute pancreatitis [18] and found that the later regimen resulted in a significantly lower rate of infectious complications and mortality [19]. The second study, again in severe acute pancreatitis, compared the effect of "rapid" (hematocrit <35%) versus "slow" (hematocrit ≥ 35%) hemodilution within 48 h of onset. The study showed that the target hematocrit of more than 35% is associated with a significantly lower rate of infectious complications and mortality [20]. Both studies suggest that aggressive fluid resuscitation in patients with severe acute pancreatitis is detrimental. The other two Chinese studies investigated colloids and crystalloids in patients with severe acute pancreatitis [21,22]. Du et al. showed that hydroxyethyl starch (HES) combined with Ringer's lactate is superior to Ringer's lactate alone in decreasing both intra-abdominal pressure and the need for mechanical ventilation [21]. Wang et al. compared three groups: early goal-directed therapy (EGDT) with HES or EGDT with HES and plasma compared to treatment with crystalloids and HES according to guidelines [22]. Patients who received a combination of EGDT, HES, and plasma had significantly better outcomes such as mortality, multiple organ dysfunction syndrome, abdominal compartment syndrome, length of stay in the intensive care unit, and need for mechanical ventilation. None of these RCTs presented any power calculations and, in the study by Wang et al. [22], the total amount of fluids given was not accounted for in the EGDT protocol. It is also worth mentioning that administration of HES to critically ill patients is controversial due to safety concerns demonstrated in several recent studies [23]. In the study by Du et al. [21], no significant difference in kidney failure or coagulopathy was found between compared groups. Wang et al. [22] did not present any data regarding possible complications related to HES administration and the subject is not discussed. In 2011, Wu et al. conducted an open label, 4-arm factorial design randomized controlled trial investigating a EGDT protocol (primary endpoint), and also comparing Ringer's lactate with normal saline [24]. At interim analysis, the study proved to be underpowered for the primary endpoint and no difference was found between the goal-directed and standard resuscitation arms in terms of systemic inflammatory response syndrome (SIRS). A significant reduction of SIRS and C-reactive protein at 24 h in the group receiving Ringer's lactate was demonstrated, however, these were only surrogate markers of clinically relevant outcomes. The sixth RCT compared administration of Ringer's lactate naso-jejunally versus intravenously in patients with predicted severe course [25]. The study outcomes were mortality, persistent organ failure, pancreatic necrosis, local complications intra-abdominal pressure, need for interventions, none of which differed significantly between the groups. There was no power calculation done and it is likely that the study was underpowered.

There is thus no high quality evidence from RCTs regarding the optimal resuscitation fluid (although Ringer's lactate appears to be promising), the required fluid rate, or the best marker to guide fluid therapy and indicate the adequacy of resuscitation (Table 2). It is not even known whether colloids or crystalloids are more effective in improving pancreatic microcirculation and outcome [26]. The initial goal of fluid resuscitation is to restore circulating blood volume with the aim of improving peripheral tissue oxygenation. Easy clinical markers of adequate hemodynamic function are heart rate, blood pressure, respiratory rate, O_2 saturation and urine output [27,28]. Urine output should be restored at above 0.5 mL/h/kg bodyweight. Hematocrit, blood urea nitrogen, creatinine and lactate are laboratory markers of volemia and adequate tissue perfusion, and should be monitored. Central venous pressure and Swan-Ganz monitoring have not been proven to be useful to guide fluid resuscitation in acute conditions [29]. Assessing volume stroke after a fluid challenge has been advocated as a major tool for monitoring the need for aggressive fluid resuscitation in critical patients [28]. However, the only RCT attempting to study the effects of early goal-directed fluid therapy (mainly based on repeated measurements of plasma blood urea nitrogen levels) on outcomes of acute pancreatitis showed negative results [24]. Based on the current best evidence, it appears that fluid resuscitation with more than 10–15 ml kg^{-1} should be discouraged; Ringer's lactate may be associated with anti-inflammatory effect; and the value of early goal-directed therapy in patients with acute pancreatitis remains unknown.

4. Antibiotics

While the use of broad-spectrum antibiotics to treat confirmed infection in acute pancreatitis is a well-established practice, the use of prophylactic antibiotics has been controversial for decades. Three RCTs in the 1970s failed to demonstrate a beneficial effect of antibiotic prophylaxis, probably due to a small sample size, inappropriate selection of antibiotics (e.g. ampicillin, which does not sufficiently penetrate the pancreas) and inclusion of patients with mild pancreatitis [30–32]. Between 1993 and 2009, several randomized controlled open label trials were published evaluating the efficacy of prophylactic antibiotic treatment in patients with severe acute pancreatitis [33–39]. The results of these trials were conflicting. While some RCTs demonstrated reduction of infectious complications and mortality with the use of prophylactic antibiotics, the others failed to do so. Only three double-blind, placebo-controlled randomized trials were published between 2004 and 2009 and all of them were unable to show a beneficial effect of antibiotic prophylaxis in regard to infectious pancreatic complications, the need for surgery, and mortality [40–42] (Table 3). This is in line with the findings of a meta-analysis that showed an inverse relationship between methodological quality of the studies and impact of antibiotic prophylaxis on mortality [43]. On the other hand, it is worth noting that the three double-blind RCTs mentioned were not without flaws. These include a large crossover to open label antibiotics in the control group (i.e. a high percentage of patients in the placebo group who were treated with intravenous antibiotics) and the inclusion of patients on the basis of "predicted" severity of acute pancreatitis rather than proven necrotizing pancreatitis. All of the studies were underpowered since the power calculation was based on an infection rate of 40%, whereas the actual infection rates in the placebo groups of the trials were only 12–17%.

There have been several attempts to statistically aggregate the data on the use of prophylactic antibiotics in acute pancreatitis. While only two new RCTs were published in 2006–2007, it is notable that 7 of the 10 meta-analyses were published within

Table 2
Randomized controlled trials of fluid resuscitation in patients with acute pancreatitis.

Study ID	Year	Setting	Intervention group	Control group	No. of patients			Allocation concealment	Outcome	Comments
					Intervention group	Control group				
Mao et al. [19]	2009	China	Rapid fluid resuscitation[1]	Slow fluid resuscitaion[2]	36		40	Open-label	Significantly higher mortality, ACS, infection rate and ventilator rate in the rapid group	SAP only. No power calculation
Mao et al. [20]	2010	China	Rapid fluid resucitation[3]	Slow fluid resuscitaion[4]	56		59	Open-label	Significantly higher mortality and infection rate in the rapid group	SAP only. No power calculation
Du XJ et al [21]	2011	China	HES	Ringer's lactate	20		21	Open-label	Significantly lower IAP and IAH and % mechanical ventilation in the HES group.	SAP only. No power calculation
Wang et al [22]	2013	China	EGDT 1	Ringer's lactate or normal saline + HES	EGDT 1	EGDT2	68	Open-label	EGDT 2 had significantly lower mortality, ACS, MODS, days on ventilator.	SAP only. No power calculation. Amount of fluids not reported.
			HES		64	68				
Wu B et al [24]	2011	USA	Goal directed resuscitation[5]	Standard resuscitation[6]	19		21	Open-label	No difference between the arms. Similar volumes.	Primary outcome: change in SIRS. Trial halted due to the low incidence of SIRS.
Wu B et al [24]	2011	USA	Lactated Ringer's solution	Normal saline	19		21	Open-label	Significant reduction in SIRS and CRP at 24 hours with lactated Ringer's solution	Secondary outcome: CRP level at 24 hours
Sharma et al[25]	2016	India	Oral hydration solution (NJ)	Ringer's lactate (i.v.)	24		25	Single-blind	No difference between the arms	Patients with predicted SAP. No power calculation.

Abbreviations: ACS: Abdominal Compartment Syndrome.
SAP: Severe Acute Pancreatitis.
HES: Hydroxyethyl starch.
IAP: Intra abdominal pressure.
IAH: Intra- abdominal hypertension.
EGDT: Early goal-directed therapy.
MODS: Multiple Organ Dysfunction Syndrome.
SIRS: Systemic Inflammatory Response Syndrome.
CRP: C-reactive protein.
NJ: Naso-jejunal.

[1] Defined as 10–15 ml/(kg ·hour).
[2] Defined as 5–10 ml/(kg·hour).
[3] Defined as goal-hematocrit <35% within 48 hours.
[4] Defined as goal-hematocrit ≥35% within 48 hours.
[5] Goal directed resuscitation: 20 mL/kg fluid i.v. for 30 min followed by 3 mL/kg/hour continuously i.v. Unchanged BUN-level after 8–12 hours followed by second fluid challenge of 20 mL/kg for 30 min. Decreased BUN-level after 8–12 hours followed by 1.5 mL/kg/hour continuously i.v.
[6] Standard Resuscitation: fluid management adjusted by treating physician.

Table 3
Randomized controlled trials of intravenous antibiotic prophylaxis versus no antibiotics in patients with acute pancreatitis.

Study ID	Year	Setting	Intervention group	Control group	No. of patients		Allocation concealment	Main findings
					Intervention group	Control group		
Howes et al. [30]	1975	USA	Ampicillin	None	48	47	Open-label	No significant difference in any outcome
Craig et al. [31]	1975	USA	Ampicillin	None			Open-label	No significant difference in any outcome
Finch et al. [32]	1976	USA	Ampicillin	Placebo	31	27	Double-blind	No significant difference in any outcome
Pederzoli et al. [33]	1993	Italy	Imipenem	None	41	33	Open-label	Significantly lower rate of pancreatic infection in the intervention group
Sainio et al. [34]	1995	Finland	Cefuroxime	None	30	30	Open-label	Significantly lower mortality rate but not pancreatic infection, in the intervention group
Delcenserie et al. [35]	1996	France	Ceftazidime + amikacin + metronidazole	None	11	12	Open-label	No significant difference in any outcome
Schwarz et al. [36]	1997	Germany	Ofloxacin + metronidazole	None	13	13	Open-label	No significant difference in any outcome
Spicak et al. [37]	2003	Czech Republic	Meropenem	None	20	21	Open-label	No significant difference in any outcome
Isenmann et al. [40]	2004	Germany	Ciprofloxacin + metronidazole	Placebo	58	56	Double-blind	No significant difference in any outcome
Dellinger et al. [41]	2007	North America and Europe	Meropenem	Placebo	50	50	Double-blind	No significant difference in any outcome
Rokke et al. [38]	2007	Norway	Imipenem	None	36	37	Open-label	Significantly lower rate of pancreatic and extrapancreatic infection in the intervention group
Xue et al. [39]	2009	China	Imipenem	None	29	27	Open-label	No significant difference in any outcome
García-Barrasa et al. [42]	2009	Spain	Ciprofloxacin	Placebo	22	19	Double-blind	No significant difference in any outcome

this period [44]. There were 13 different RCTs included in the 7 meta-analyses. Because of different inclusion criteria and various meta-analytic techniques used, there was a lack of concordance and they provided contradictory recommendations regarding the role of prophylactic antibiotics in reducing the risk of pancreatic infectious complications. Overall, it appears that the most recent studies do not support the use of prophylactic antibiotics to reduce the frequency of pancreatic infectious complications, surgical intervention, and mortality in patients with acute pancreatitis. Routine broad-spectrum prophylactic antibiotics in patients with acute pancreatitis cannot be recommended on the basis of the best current evidence.

5. Nutritional management

5.1. Oral refeeding

The usual criteria for hospital discharge of patients with acute pancreatitis are the resolution of pain and the tolerance of oral refeeding. The conventional management of acute pancreatitis involves a nil per *os* regimen until signs and symptoms of acute pancreatitis are solved. This approach is based on the hypothesis that oral intake in the early phase of acute pancreatitis will stimulate synthesis and secretion of pancreatic enzymes, increase intrapancreatic enzyme activation and thus increase pancreatic tissue damage. Traditionally, refeeding is initiated with oral intake of clear fluids, followed by soft and solid oral food, as tolerated. However, there is growing evidence that questions the rationale for 'pancreas rest' as a mainstay in the management of acute pancreatitis [45]. And the three emerging questions related to oral feeding are what to feed, when to feed, and who governs these feeding decisions. These questions are reviewed in detail elsewhere [46,47] and are beyond the scope of this article.

5.2. Type of nutritional support

The importance and feasibility of providing nutritional support in patients with acute pancreatitis has been known for more than 5 decades. Parenteral nutrition (PN), rather than enteral nutrition (EN), became the standard of care because it was considered important for 'pancreas rest'. The rationale was to prevent stimulating increased pancreatic secretion of proteolytic enzymes and thereby exacerbating the severity of pancreatitis. The reliance on PN has decreased in response to an increased awareness of attendant problems, such as catheter-related sepsis, the high cost of treatment, electrolyte and metabolic disturbances, villous atrophy and gut barrier failure with promotion of bacterial translocation, systemic sepsis and multiple organ failure.

A number of RCTs compared total PN and total EN in the management of predicted severe acute pancreatitis (Table 4) [48–59]. Two meta-analyses of high-quality RCTs have shown a significant 2-fold reduction in the risk of total and pancreatic infectious complications and a 2.5 fold reduction in the risk of death in patients receiving total EN [60,61]. Meta-analyses of RCTs evaluating the effect of pharmaconutrition-supplemented PN showed some beneficial effects in comparison with total PN [62,63]. However, it is unlikely that supplemented PN offers any benefit in comparison with total EN.

5.3. Route of enteral feeding

Nasogastric (NG) tube insertion appears to be the best current initial approach to enteral feeding as nasojejunal (NJ) tube insertion often requires endoscopy or radiology expertise for insertion and may cause a delay to commence feeding. Over the past few decades, NJ EN has been preferred to NG EN because of the concern that more proximal feeding would result in pancreatic stimulation and more severe pancreatitis. NG or duodenal feeding has been believed to increase the chances of aspiration pneumonitis and to stimulate pancreatic secretion resulting in inefficient restoration of gut mucosal integrity, whereas NJ feeding has not. The pancreatic enzyme response to enteral feeding was studied in human volunteers and it was shown that all forms of EN, with the exception of NJ feeding, stimulate pancreatic secretion [64]. By contrast, a study in patients with acute pancreatitis showed a significantly lower rate of secretion of trypsin, amylase and lipase in comparison with healthy subjects [65]. Moreover, it was shown that pancreatic enzyme secretion in response to duodenal feeding was less in patients with more severe pancreatitis, probably reflecting a greater injury to the acinar cell mass.

There have been three RCTs directly comparing NG EN with NJ EN in patients with predicted severe acute pancreatitis [66–68]. These demonstrated the feasibility, safety, and tolerance of NG EN and showed no evidence of increased complications associated with the introduction of NG feeding compared with the NJ route. Further, two meta-analyses showed no significant difference in the incidence of mortality, tracheal aspiration, and exacerbation of pain between the two routes of feeding [69,70].

5.4. Type of enteral feed

The concept of 'pancreas rest' has also influenced decisions about the type of feed given during EN. Feeds, such as (semi)-elemental formulae, have been preferred because they did not require pancreatic enzymes for digestion and absorption [71]. However, the major disadvantage of (semi)-elemental formulae is the cost, which is reportedly 3-7 fold higher than that of polymeric formulae. A recent meta-analysis of RCTs compared these two types of formulae in terms of feeding intolerance, infectious complications, mortality and found that the use of polymeric over elemental feeding formulae did not result in reduced feeding tolerance in patients with acute pancreatitis and appeared to reduce the risk of infectious complications and mortality [72]. Thus, the use of semi-elemental and elemental formulae confers no apparent advantage over relatively inexpensive polymeric formulae.

It has also been considered that the use of immune-enhanced enteral formulations might increase the beneficial effects of EN in acute pancreatitis [73]. Several trials in different clinical settings have suggested that immuno-nutrition might confer benefit by modifying the inflammatory response. The results of RCTs that compared the use of immune-enhanced and standard enteral formulae were statistically aggregated in several meta-analyses [74–76]. The most recent and comprehensive systematic review of 2419 patients from 22 RCTs [76] found that the benefits of immune-enhancing EN may depend on the subset of the analyzed patients. There was no benefit of immunonutrition on the risk of infectious complications or mortality within the subset of critically ill patients. At the same time, administration of high-arginine-content formulae in a combined group of critically ill and elective surgery patients was associated with a statistically significant reduction in infectious complications and a trend to a lower mortality in comparison with other immune-enhancing diets. A meta-analysis of RCTs in patients with acute pancreatitis did not show any clinical beneficial effect of immunonutrition, when compared with standard EN [77]. A recent RCT, not included in the meta-analysis mentioned above, studied the effect of EN combined with rhubarb (a common herb used in Chinese medicine) and it showed that, compared with total EN, patients in the intervention group had a reduced length of hospitalization and improved gastrointestinal function [78].

Table 4
Randomized controlled trials of total enteral versus total parenteral nutrition in patients with acute pancreatitis.

Study ID	Year	Setting	Intervention group	Control group	No. of patients		Allocation concealment	Reduction of infectious complications and mortality
					Intervention group	Control group		
Kalfarentzos et al. [48]	1997	Greece	Enteral nutrition	Parenteral nutrition	18	20	Open-label	Significantly lower rate of pancreatic infection in the intervention group
McClave et al. [57]	1997	USA	Enteral nutrition	Parenteral nutrition	16	16	Open label	No significant difference in the outcomes
Olah et al. [56]	2002	Hungary	Enteral nutrition	Parenteral nutrition	41	48	Open-label	Non-significantly lower rate of sepsis and mortality in the intervention group
Abou-Assi et al. [58]	2002	USA	Enteral nutrition	Parenteral nuntrition	26	27	Open-label	No significant difference in the outcomes
Gupta et al. [49]	2003	UK	Enteral nutrition	Parenteral nutrition	8	9	Open-label	Non-significantly lower rate of pancreatic infection in the intervention group
Louie et al. [50]	2005	Canada	Enteral nutrition	Parenteral nutrition	10	18	Open-label	Non-significantly lower rate of pancreatic infection in the intervention group
Eckerwall et al. [51]	2006	Sweden	Enteral nutrition	Parenteral nutrition	23	25	Open-label	No significant difference in the outcomes
Petrov et al. [52]	2006	Russia	Enteral nutrition	Parenteral nutrition	35	34	Open-label	Significantly lower rate of pancreatic infection and mortality in the intervention group
Casas et al. [53]	2007	Spain	Enteral nutrition	Parenteral nutrition	11	11	Open-label	Non-significantly lower rate of pancreatic infection in the intervention group
Doley et al. [54]	2008	India	Enteral nutrition	Parenteral nutrition	25	25	Open-label	No significant difference in the outcomes
Qin et al. [59]	2008	China	Enteral nutrition	Parenteral nutrition	36	38	Single-blind	Significantly lower rate of multiple organ failure in the intervention group
Wu et al. [55]	2010	China	Enteral nutrition	Parenteral nutrition	53	54	Open-label	Significantly lower rate of pancreatic infection and mortality in the intervention group

Table 5
Recommendations for early management of patients with acute pancreatitis.

	Do's	Don'ts
Analgesics	Follow local guidelines for acute pain management in the perioperative setting	Abstain from analgesia completely in the first 24 hours of hospitalisation
Fluids	Prefer lactated Ringer's solution to isotonic crystalloid	Use aggressive fluid resuscitation protocols
Antibiotics	Administer antibiotics in patient with confirmed (peri)pancreatic infected necrosis	Administer antibiotics with the aim of prophylaxis
Nutrition	Commence nasogastric tube feeding in 24–48 hours after hospital admission in patients with organ dysfunction and/or (peri)pancreatic necrosis	Feed any patient with acute pancreatitis within 24 hours of hospitalisation
	Reserve nasojejunal tube feeding to patients who cannot tolerate gastric feeding	Determine the need for tube feeding based on predicted criteria of severity (e.g. APACHE II score, C-reactive protein)
ERCP	In patients with co-existing acute cholangitis only	Determine the need for ERCP based on predicted criteria of severity

Abbreviations: APACHE, acute physiology and chronic health evaluation; ERCP, endoscopic retrograde cholangiopancreatography.

5.5. Timing of enteral feeding

The indirect evidence from the trials of EN versus PN is inconsistent with respect to when is the best time to commence feeding [79]. Some authors have demonstrated clinical benefits of early EN compared to delayed EN in terms of lower incidence of multi-organ distress syndrome, SIRS, pancreatic infectious complications, and shorter ICU stay but no difference in the mortality rate [80].

A RCT from New Zealand showed that starting NG EN within 24 h of hospital admission results in a significant decrease in the intensity and duration of abdominal pain and risk of oral food intolerance [81]. On the other hand, a Dutch study showed no superiority of early EN in patients with AP [82]. However, it is worth noting that the actual site of feeding in the Dutch study is unclear as tubes were dislodged in 40% of the patients. Further, only one third of the patients had actual, as opposed to predicted, severe or critical AP (i.e., persistent organ failure, infected pancreatic necrosis, or both). Hence, two-thirds of the patients in that study were not posed at the outset to benefit from tube feeding. The possible benefits of early nutrition are maintaining the gut integrity (enterocyte population) and function (motility) and reducing bacterial translocation and ileus, and these may also help to achieve caloric targets more quickly [83,84]. However, early nutrition is not without risk, particularly in hemodynamically unstable patients and those requiring inotropic support [26]. These patients appear to be at an increased risk of non-occlusive mesenteric ischemia, and it is best to commence EN after the patient has been adequately resuscitated [27]. As a guideline, feeding of patients with acute pancreatitis should, in general, be started on the second day after hospital admission—enteral tube feeding in patients with gut dysfunction and oral refeeding in patients with normal gut function [85]

Two recent meta-analyses have shown that early EN (started within 48 h of admission), in comparison with late EN or PN, resulted in statistically significant reduction in the risks of organ failure, pancreatic infections, and mortality [86,87].

6. Therapeutic ERCP

Endoscopic retrograde cholangiopancreatography (ERCP) with sphincterotomy (ES) was promoted as a beneficial intervention in patients with acute biliary pancreatitis in the early 1990s. This was based on the findings of two RCTs, from the UK and Hong Kong, of early (within 24–48 h of admission) ERCP ± ES versus conservative treatment [88,89]. Both trials demonstrated that early ERCP was associated with a reduction in complications but not mortality, but the benefits were only apparent in patients with predicted severe acute pancreatitis. There is some evidence to suggest that the duration of biliary obstruction, rather than the predicted severity of acute pancreatitis, is the most important determinant of outcome [90,91]. This is probably due to the increased likelihood of concomitant cholangitis with prolonged obstruction and might be the best explanation for the usefulness of ERCP in the management of acute biliary pancreatitis [92]. The first multicentre RCT to examine the role of ERCP in acute pancreatitis was designed to include only patients with evidence of biliary obstruction, defined by clinical and radiological criteria [93]. This German study did not find any benefit for early ERCP (within 72 h after onset of symptoms) over conservative treatment.

A subsequent RCT from Argentina found that early ERCP in patients with biliary obstruction, defined by laboratory and radiological criteria, and without evidence of acute cholangitis, conferred no benefit [94]. Two important meta-analyses were published in 2008. The first found that early ERCP, compared with conservative treatment in patients with both predicted mild and predicted severe acute pancreatitis, did not decrease the incidence of local pancreatic complications or mortality rate [95]. The second meta-analysis was designed to negate the confounding effect of acute cholangitis and demonstrated no benefit of early ERCP over conservative treatment in terms of complications and mortality in patients with predicted mild and predicted severe AP [96]. The conclusion to be drawn from these studies is that early ERCP is indicated in patients with acute pancreatitis if there is clinical evidence of acute cholangitis, but not for those with cholestasis alone [92]. While cholestasis can reflect a persisting common bile duct stone, it might also be due to oedema of the ampulla secondary to recent stone passage to the duodenum and thus be expected to improve over the first few days of admission. Persistent cholestasis without cholangitis, may require an ERCP, but not usually in the acute setting.

7. Conclusions

While specific treatments for acute pancreatitis that address critical and outcome determining pathophysiology are awaited and there is no clinically useful laboratory marker yet to monitor the clinical trajectory of patients [97,98], there has been accumulation of new evidence pertinent to early management of acute pancreatitis. Surgical management of acute pancreatitis is being applied to fewer patients and there has been a notable trend towards less invasive approaches. There have also been important advances in the non-surgical management of acute pancreatitis, particularly in the more appropriate and effective use of antibiotics, nutritional management, and endoscopic biliary decompression (Table 5). There is a need for more high quality trials to determine the best strategies for pain relief and fluid resuscitation.

Conflicts of interest
None declared.

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