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STATE OF THE ART

Management of Acute Pancreatitis in the Early Stage

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ABSTRACT

Acute pancreatitis (AP) is a potential fatal disease with an overall mortality around 5%. The current treatment for AP relies on supportive medical therapy, sometimes associated with endoscopic procedures and/or surgical interventions. In this review we discuss the recent concepts regarding the fluid therapy, pain management, antibiotic prophylaxis, apheresis for hypertriglyceridemia-induced AP, timing and indications for ERCP and cholecystectomy in biliary AP. For each component, the importance and the impact of early phase treatment is presented in terms of benefits and risks.

Keywords: acute pancreatitis, early phase, early treatment, fluid therapy, nutrition, ERCP

INTRODUCTION

Despite tremendous advances in pathophysiology, imaging, and intensive care treatment during the last decades, acute pancreatitis remains a potentially lethal disease with an unpredictable evolution. The new revision of Atlanta classification stratifies the acute pancreatitis in three grades of severity: mild, moderate and severe (1). Despite a high mortality for the severe cases around 50%, due to higher prevalence of mild and moderate cases one can explain the global rate of mortality in acute pancreatitis around 5%. The early phase of acute pancreatitis is defined by the same classification as the first 7 days from onset (can be extended to 10-14 days). Almost 50% of deaths from acute pancreatitis occur during this phase due to SIRS and multiple organ failure (1,2). Therefore, a correct and energetic treatment during this period is crucial to reduce early deaths and to optimize evolution of predicted severe forms. The purpose of the present article is to review the significance and impact of the current early treatment of acute pancreatitis. ❑

FLUID RESUSCITATION

One important step in the pathogenesis of acute pancreatitis is represented by alteration of the pancreatic microcirculation including ischemia-reperfusion injury and microthrombi that can lead to ischemia and later to necrosis. These changes are most marked in

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the first 24 to 72 hours of the illness. Therefore the theoretical goal of the early intravenous fluid resuscitation is to prevent or even to reverse these alterations, leading to improve morbidity and mortality (3). Hemoconcentration as hematocrit of >44-47% on admission along with failure to decrease it after 24 hours was reported as a good risk factor for development of necrosis (4). Clinical practice guidelines recommend vigorous fluid resuscitation, but the optimal type of fluid, rate of administration and end-points of adequate resuscitation are still without consensus (5).

The recommended rate of fluid resuscitation is 250-500 mL/h for the first 24-48 hours (6,7). However, several reports showed that overly aggressive fluid therapy fluid therapy is associated with increased morbidity and mortality (8,9). One prospective trial analyzed 247 patients showed that administration of more than 4100 mL fluids during the first 24 hours was associated with higher incidence of persistent organ failure and acute collections, compared with volumes between 3100 and 4100 mL (10). For this reason the total amount for the first 24 hours is not recommended to exceed 4000 mL (11). Instead of firm rate for fluid resuscitation was suggested to start as a bolus followed by maintenance (7). The Pittsburgh group is using a bolus of 1000-2000 mL of Lactated Ringer's (or 20 mL/Kg) in the emergency room, followed by 3 mL/kg/hour for the first 24 hours (12). The effectiveness of fluid therapy can be also improved by using a "controlled" resuscitation in order to maintain effective mean arterial pressure and urine output >0.5 mL/Kg (13).

The optimum type of fluid is considered the lactated Ringer's solution (6, 11). One double-blinded randomized controlled study including 40 patients with 4 arms (early-directed fluid therapy vs standard therapy and further normal saline vs lactated Ringer's solution) showed that lactated Ringer's group was associated with lower SIRS frequency (84% vs 0%, $p = 0.035$) and lower CRP level (51.5 vs 104 mg/dL, $p = 0.02$) (14).

In conclusion, fluid therapy in acute pancreatitis can be seen as double edge sword with risk of necrosis through tissue hypoperfusion by using low fluid quantities and liquid sequestration and increased morbidity with too high volumes (15). Therefore a safe and effective approach for fluid therapy for patients with acute pancreatitis should be most probably an individualized protocol. ❑

PAIN MANAGEMENT

The most common and significant complain leading to the diagnosis of acute pancreatitis is pain and therefore adequate analgesia represents an important part of the treatment. In relation to severity of the pain one can use parenteral (nonsteroidal anti-inflammatory drugs, opioid analgesics and local anesthetic) and epidural analgesia (16). One experimental prospective study assessed the effect of sympathetic block by thoracic epidural anesthesia founded enhanced microcirculatory perfusion, end-organ perfusion and improved survival compared to control (17). However these positive experimental results are not automatically transposed in humans and several concerns were addressed (18). Despite historical reports of spasm in the sphincter of Oddi associated with opioids treatment of AP, a recent Cochrane review on five RCTs with a total of 227 patients founded no difference between opioids and other analgesia options regarding the risk of complications or clinically serious adverse events (19). ❑

PROPHYLACTIC ANTIBIOTICS

The most common cause of late death in acute necrotizing pancreatitis is represented by organ failure through infected pancreatic necrosis (IPN) (20,21). Therefore there might be a theoretical benefit from antibiotic prophylaxis. For successful antibiotic treatment there should be considered the microbial pathogens causing IPN (most commonly *Escherichia coli, Pseudomonas, Klebsiella, Enterococcus* and more rarely fungi), pathogenesis of IPN (bacterial translocation through gastrointestinal mucosal barrier, altered gastrointestinal motility) and the pancreatic penetration of the antibiotics (most effective carbapenems and quinolones). However one must also consider risks associated with antibiotics use: selection of resistant bacteria, development of fungal infection, Clostridium difficile infection (22,23).

There are many RCTs and meta-analyses assessing the benefits of antibiotic prophylaxis in patients with acute pancreatitis, with contradictory results mostly due to differences in methodological design (24). As a matter of fact, the numbers of RCTs and meta-analyses on this

topic are comparable. With few exceptions (25,26), most of the meta-analyses failed to show a significant benefit effect from antibiotic prophylaxis on IPN and mortality (27-30). In one meta-analysis was showed that one needs to treat 1429 patients for one to benefit (29). The current guideline is not supporting the use of prophylactic antibiotics for the early phase of acute pancreatitis, even in predicted severe cases (11). There is no enough data to support the prevention of fungal infections and therefore is not recommended. ❑

NUTRITION

Prolonged bowel rest by nothing per os (NPO) to minimize pancreatic secretion was an important part of the therapy for any patient with acute pancreatitis. The concept of nutritional support in AP has gradually moved towards enteral feeding, due to large evidence proving safety and efficiency (31). Timing and mode of nutritional support in acute pancreatitis should be based on risk prediction of severity.

Several RCTs on mild acute pancreatitis suggested that oral feeding can be started immediately (32), directly with solids (33) and without waiting to normalize the lipase level (34). However, a more recent retrospective study on 323 patients with mild acute pancreatitis showed a rate of 12.4% intolerance to early refeeding (35). The multivariate logistic regression analysis of this study identified three factors that independently predicted refeeding intolerance: hypertriglyceridemia induced AP, elevated serum lipase (>2-fold of the upper limit of normal) the day before refeeding and the immediate feeding. The IAP/APA guidelines recommends that for mild AP the oral feeding can be started when symptoms are decreasing and the inflammatory markers are improving (11).

Enteral nutrition (EN) besides providing nutritional support, can preserve the gut function and potentially modulates the systemic inflammatory response syndrome (SIRS) that is associated with higher morbidity and mortality (36, 37). For this reason, patients with predicted severe acute pancreatitis should have a potential benefit from using enteral nutrition. A systematic meta-analysis involving 11 randomized controlled trials demonstrated a significantly reduced risk of multiple organ failure (RR 0.44; 95 % CI 0.23, 0.84), pancreatic infectious complications (RR 0.46; 95 % CI 0.27, 0.77) and mortality (RR 0.46; 95 % CI 0.20, 0.99) in patients with acute pancreatitis who were enterally fed within the first 48 h of admission compared to parenteral feeding (38).

Enteral feeding can be started at a slow rate of 25mL/hour with elemental nutrient or polymeric formula for the first 24 hours, followed by gradual advanced by 25 mL/hour over the next 2-3 days. Both variants are safe according to one meta-analysis (39). There are currently several discussions about the moment and the method of enteral feeding. Enteral nutrition can be provided via nasogastric (NG) or nasojejunal (NJ). Despite of theoretical risk of pancreatic stimulation with NG, there are two RCT that showed that both routes are well tolerated with no difference in terms of infectious complications, length of hospital stay or mortality (40,41). A meta-analysis of four studies showed that NG feeding is efficient in 90% of patients with severe acute pancreatitis (42).

A retrospective study in a single institution have evaluated the optimal time of refeeding in severe acute pancreatitis comparing 526 patients in the early group versus 566 patients in the late group (43). The incidence of organ failure and mortality were statistically significant better for the early feeding group. The PYTHON trial performed by the Dutch Pancreatitis Study Group was a multicenter RCT that compared nasoenteric tube feeding initiated within 24 hours after randomization (the early group, 101 patients) or to an oral diet starting at 72 hours (the on-demand group, 104 patients) (44). This trial failed to show the superiority of early nasoenteric tube feeding due to similar rate of major infection (25% and 26%, respectively; $p = 0.87$), multiple organ failure (10% and 8%, respectively; $p = 0.77$), persistent multiple organ failure (6% and 5%, respectively; $p = 1.00$), or death (11% and 7%, respectively; $p = 0.33$). Another controlled RCT assessed the effectiveness and feasibility of early oral refeeding (EORF) based on hunger in 146 patients with moderate or severe acute pancreatitis (45). There was no difference in the number of adverse events or complications between the EORF and the conventional oral refeeding group. The results of this study showed that EORF is safe and effective, decreasing the length of hospital stay by 2 days.

Acute pancreatitis can be associated with intestinal ileus and delayed gastric emptying

that can lead to abdominal pain, nausea and vomiting which can make intolerance oral feeding, prompting for parenteral support. Also patients that have intolerance for enteral feeding and nutritional support is required should start parenteral feeding as second-line therapy (11). Despite theoretical benefits of probiotic prophylaxis for patients with predicted severe acute pancreatitis, mortality was increased (16% vs 6%) in one RCT and therefore not indicated (46). ❑

APHERESIS

Hypertriglyceridemia with serum triglyceride (TG) level of >1000 mg/dl is a well-recognized cause of acute pancreatitis (AP), representing the third identifiable etiology after gallstones and alcohol. Classical treatment of hypertriglyceridemia induced AP includes heparin, insulin or both. A more effective modality to reduce the TG level is represented by apheresis techniques. A recent systematic review including 301 patients founded a 85.4% reduction of the TG level using apheresis (47). The same study founded that 94.4% of patients were reported to have some form of improvement, with 93.1% improvement in severe acute pancreatitis and 88% with organ failure (47). The use of apheresis in patients with hypertriglyceridemia induced AP can be individualized according to level of TG at admission (>1000 mg/dL or >2000 mg/dL), timing of initiation (up to 96 hours after the onset of symptoms), number of sessions (unique or multiple), use of adjunct therapy (insulin, heparin, fibrate). ❑

ENDOSCOPIC RETROGRADE COLANGIOPANCREATOGRAPHY (ERCP)

Around one third of the etiology of acute pancreatitis is represented by gallstones and the ERCP can be used as both diagnostic and therapeutic tool as well. However the procedure of ERCP associated with endoscopic sphincterotomy (ES) can lead to adverse events and therefore the indication should not be liberal. Several randomized controlled trials (RCT) have been published (Table 1) to define the role and indications of ERCP and ES for patients with acute pancreatitis. One must note that there is some degree of heterogeneity among these studies due to different inclusion and exclusion criteria, definition of severity of pancreatitis and timing to ERCP.

One meta-analysis including 644 patients with acute gallstone pancreatitis showed no evidence that early routine ERCP significantly improve local/systemic complications or mortality, regardless of predicted severity (48). The current indications for the ERCP in patients with predicted severe acute pancreatitis are

First author, reference	Neoptolemos(50)	Fan(51)	Folsch(52)	Oria(53)	van Santvoort(54)
Journal, year of publication	Lancet, 1988	NEJM, 1993	NEJM, 1997	Ann Surg, 2007	Ann Surg, 2009
Number of centers	Unicentric	Unicentric	Multicenter	Unicentric	Multicenter
Inclusion criteria	Biliary acute pancreatitis	Acute pancreatitis of any etiology	Biliary acute pancreatitis	Biliary acute pancreatitis	Severe biliary acute pancreatitis
Exclusion criteria			Bilirubin >5 mg/dL	Acute cholangitis	Acute cholangitis
Number of patients ERCP	59	97	126	51	81
Number of patients control	62	98	112	52	72
Timing of ERCP	Less than 72 hours from admission	Less than 24 hours from admission	Less than 72 hours from onset	Less than 48 hours from onset	Less than 72 hours from onset
Definition of severity for AP	Modified Glasgow criteria	BUN >45 mg/dL Glu >198 mg/dL Ranson score	Modified Glasgow criteria	APACHE II score	APACHE II score Imrie score CRP >150 mg/dL
Predicted severe PA	44%	41.5%	19.3%	36.9%	100%
Morbidity (ERCP vs Conservative)	17% vs 34% (p=0.03)	18% vs 29% (p=0.07)	46% vs 51%	21% vs 18% (p=0.8)	25% vs 54%* (p=0.02) 45% vs 41%** (p=0.81)
Mortality (ERCP vs Conservative)	2% vs 8% (p=0.23)	5% vs 9% (p=0.4)	11% vs 6% (p=0.1)	6% vs 2% (P=1)	6% vs 15% (p=0.213)

TABLE 1. Summary of RCT assessing the results of ERCP in acute pancreatitis.
*patients with cholestasis; ** patients without cholestasis

co-existing biliary obstruction or cholangitis (11,48). There is a high likelihood of choledocholithiasis if bilirubin level is higher than 4mg/dL or bilirubin level between 1.8 and 4 mg/dL and dilated common bile duct on ultrasound (>6 mm, with gallbladder *in situ*) (49).

The optimal timing for ERCP is considered to be urgent (<24 hours) for patients with cholangitis; for biliary obstruction can be awaited 24-72 hours because of the possibility of spontaneous improvement. ERCP with ES can be also considered later during the same hospital admission for medical unfit patients for laparoscopic cholecystectomy (11). ❑

CHOLECYSTECTOMY FOR BILIARY ACUTE PANCREATITIS

Patients with predicted mild acute gallstone pancreatitis (AGP) can be operated (laparoscopic cholecystectomy, LC) within the same hospital admission (55). One approach uses the trend in pancreatic enzyme level to guide the timing of an operation (56). A decreasing level makes the patient suitable for surgery, while a stable or an increasing level requires delay. Two studies from the same center evaluated operated patients with mild AGP within 48 hours from admission regardless of resolution of abdominal pain or abnormal laboratory values (57,58). A retrospective analysis compared 117 patients with early LC and 186 with delayed LC. The complication rates were similar between groups, but hospital stay was longer in the second group (3 vs 6 days, p<0.001) (57). The prospective study randomized 50 patients and founded the same results (58). However caution was suggested concerning this approach (59,60).

On the other hand, for cases with predicted severe AGP, cholecystectomy should be performed after an interval of 6 weeks along with resolution of abdominal pain and abnormal laboratory values; cholecystectomy can be also combined with drainage of pancreatic fluid collection or debridement of pancreatic necrosis (11). One retrospective study of 151 patients revealed a higher incidence of infected peripancreatic fluid collections in patients who underwent early cholecystectomy after severe pancreatitis (61). The overall management of AGP is described in Figure 1. ❑

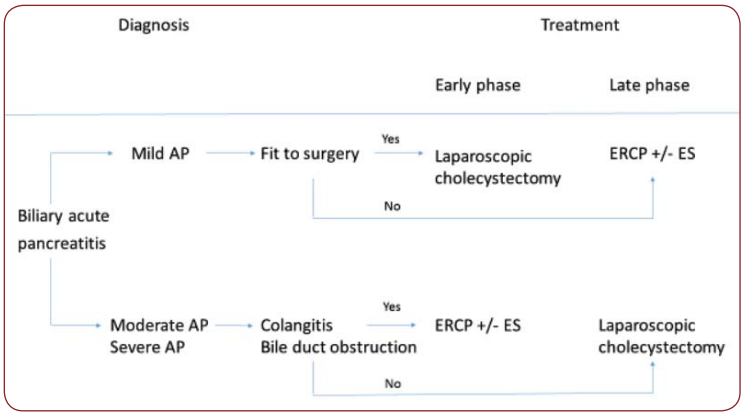

FIGURE 1. Management of acute gallstone pancreatitis.

EARLY NECROSECTOMY

One prospective trial compared early necrosectomy (48-72 hours from the onset) with late necrosectomy (after 12 days) and founded a higher mortality for the early group (58% vs 27%) and therefore the first one is not indicated (62). Current guidelines proposed a delayed (four weeks after onset of pancreatitis) interventional management for pancreatic necrosis (11). Another potential indication for early surgery is represented by abdominal compartment-syndrome that is sustained intra-abdominal pressure (measured via bladder) > 25 mmHg that is associated with new onset organ failure that is refractory to medical treatment (63). ❑

CONCLUSION

Acute pancreatitis is a potential life-threatening disease with a high mortality around 5% and the early phase represents the best window of opportunity for successful treatment. The current treatment for AP includes supportive medical therapy, endoscopic and surgical interventions. Despite different definitions for timing for each treatment component most of them revolve around 24-48 hours. This period allows an accurate diagnosis and severity stratification along with appropriate therapy. Due to multidisciplinary diagnostic and therapeutic requirements these patients should be treated by dedicated teams. Further studies are requested to better define the indications and limits of each type of therapy and to develop new classes of treatment.

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References

1. **Banks PA, Bollen TL, Dervenis C, et al. –** Classification of acute pancreatitis--2012: Revision of the atlanta classification and definitions by international consensus. *Gut* 2013;62:102-11
2. **Carnovale A, Rabitti PG, Manes G, et al. –** Mortality in acute pancreatitis: Is it an early or a late event? *JOP.* 2005;6:438-44
3. **Brown A, Baillargeon JD, Hughes MD, et al. –** Can fluid resuscitation prevent pancreatic necrosis in severe acute pancreatitis? *Pancreatology* 2002;2:104-7
4. **Brown A, Orav J, Banks PA –** Hemoconcentration is an early marker for organ failure and necrotizing pancreatitis. *Pancreas* 2000;20:367-72
5. **Aggarwal A, Manrai M, Kochhar R –** Fluid resuscitation in acute pancreatitis. *World J Gastroenterol* 2014;20:18092-103
6. **Tenner S, Baillie J, DeWitt J, et al. –** American college of gastroenterology guideline: Management of acute pancreatitis. *Am J Gastroenterol* 2013;108:1400-16
7. **Whitcomb DC –** Clinical practice. Acute pancreatitis. *N Engl J Med* 2006;354:2142-50
8. **Weitz G, Woitalla J, Wellhoner P, et al. –** Detrimental effect of high volume fluid administration in acute pancreatitis - a retrospective analysis of 391 patients. *Pancreatology* 2014;14:478-83
9. **Mao EQ, Tang YQ, Fei J, et al. –** Fluid therapy for severe acute pancreatitis in acute response stage. *Chin Med J (Engl)* 2009;122:169-73
10. **de-Madaria E, Soler-Sala G, Sanchez-Paya J, et al. –** Influence of fluid therapy on the prognosis of acute pancreatitis: A prospective cohort study. *Am J Gastroenterol* 2011;106:1843-50
11. **Working Group IAP APA APG –** IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013;13:e1-15
12. **Nasr JY, Papachristou GI –** Early fluid resuscitation in acute pancreatitis: A lot more than just fluids. *Clin Gastroenterol Hepatol* 2011;9:633-4
13. **Sarr MG –** Early fluid "resuscitation/therapy" in acute pancreatitis: Which fluid? What rate? What parameters to gauge effectiveness? *Ann Surg* 2013;257:189-90
14. **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;9:710-17 e1
15. **de-Madaria E, Garg PK –** Fluid therapy in acute pancreatitis - aggressive or adequate? Time for reappraisal. *Pancreatology* 2014;14:433-5
16. **Meng W, Yuan J, Zhang C, et al. –** Parenteral analgesics for pain relief in acute pancreatitis: A systematic review. *Pancreatology* 2013;13: 201-6
17. **Bachmann KA, Trepte CJ, Tomkotter L, et al. –** Effects of thoracic epidural anesthesia on survival and microcirculation in severe acute pancreatitis: A randomized experimental trial. *Crit Care* 2013;17:R281
18. **Harper D, McNaught CE –** The role of thoracic epidural anesthesia in severe acute pancreatitis. *Crit Care* 2014;18:106
19. **Basurto Ona X, Rigau Comas D, Urrutia G –** Opioids for acute pancreatitis pain. *Cochrane Database Syst Rev* 2013;7:CD009179
20. **Isenmann R, Rau B, Beger HG –** Bacterial infection and extent of necrosis are determinants of organ failure in patients with acute necrotizing pancreatitis. *Br J Surg* 1999;86:1020-4
21. **Beger HG, Rau B, Isenmann R –** Natural history of necrotizing pancreatitis. *Pancreatology* 2003;3:93-101
22. **Su MS, Lin MH, Zhao QH, et al. –** Clinical study of distribution and drug resistance of pathogens in patients with severe acute pancreatitis. *Chin Med J (Engl)* 2012;125:1772-6
23. **Schwender BJ, Gordon SR, Gardner TB –** Risk factors for the development of intra-abdominal fungal infections in acute pancreatitis. *Pancreas* 2015; 44:805-7
24. **de Vries AC, Besselink MG, Buskens E, et al. –** Randomized controlled trials of antibiotic prophylaxis in severe acute pancreatitis: Relationship between methodological quality and outcome. *Pancreatology* 2007;7:531-8
25. **Ukai T, Shikata S, Inoue M, et al. –** Early prophylactic antibiotics administration for acute necrotizing pancreatitis: A meta-analysis of randomized controlled trials. *J Hepatobiliary Pancreat Sci* 2015;22:316-21
26. **Yao L, Huang X, Li Y, et al. –** Prophylactic antibiotics reduce pancreatic necrosis in acute necrotizing pancreatitis: A meta-analysis of randomized trials. *Dig Surg* 2010;27:442-9
27. **Wittau M, Mayer B, Scheele J, et al. –** Systematic review and meta-analysis of antibiotic prophylaxis in severe acute pancreatitis. *Scand J Gastroenterol* 2011;46:261-70
28. **Villatoro E, Mulla M, Larvin M –** Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev* 2010: CD002941
29. **Jiang K, Huang W, Yang XN, et al. –** Present and future of prophylactic antibiotics for severe acute pancreatitis. *World J Gastroenterol* 2012;18:279-84
30. **Jafri NS, Mahid SS, Idstein SR, et al. –** Antibiotic prophylaxis is not protective in severe acute pancreatitis: A systematic review and meta-analysis. *Am J Surg* 2009;197:806-13
31. **Olah A, Romics L Jr. –** Enteral nutrition in acute pancreatitis: A review of the current evidence. *World J Gastroenterol* 2014;20:16123-31
32. **Eckerwall GE, Tingstedt BB, Bergenzaun PE, et al. –** Immediate oral feeding in patients with mild acute pancreatitis is safe and may accelerate recovery--a randomized clinical study. *Clin Nutr* 2007;26:758-63
33. **Moraes JM, Felga GE, Chebli LA, et al. –** A full solid diet as the initial meal in mild acute pancreatitis is safe and result in a shorter length of hospitalization: Results from a prospective, randomized, controlled, double-blind clinical trial. *J Clin Gastroenterol* 2010;44:517-22
34. **Teich N, Aghdassi A, Fischer J, et al. –** Optimal timing of oral refeeding in mild acute pancreatitis: Results of an open randomized multicenter trial. *Pancreas* 2010;39:1088-92
35. **Ren T, Shi Z, Tang J, et al. –** Risk factors of refeeding intolerance in mild acute interstitial pancreatitis: A retrospective study of 323 patients. *Pancreatology* 2015
36. **Hegazi RA, DeWitt T –** Enteral nutrition and immune modulation of acute pancreatitis. *World J Gastroenterol* 2014;20:16101-5
37. **Sun JK, Mu XW, Li WQ, et al. –** Effects of early enteral nutrition on immune function of severe acute pancreatitis patients. *World J Gastroenterol* 2013;19:917-22
38. **Petrov MS, Pylypchuk RD, Uchugina AF –** A systematic review on the timing of artificial nutrition in acute pancreatitis. *Br J Nutr* 2009;101:787-93
39. **Petrov MS, Loveday BP, Pylypchuk RD, et al. –** Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis. *Br J Surg* 2009;96:1243-52
40. **Eatock FC, Chong P, Menezes N, et al. –** A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *Am J Gastroenterol* 2005;100:432-9
41. **Kumar A, Singh N, Prakash S, et al. –** Early enteral nutrition in severe acute pancreatitis: A prospective randomized controlled trial comparing nasojejunal and nasogastric routes. *J Clin Gastroenterol* 2006;40:431-4
42. **Nally DM, Kelly EG, Clarke M, et al. –** Nasogastric nutrition is efficacious in severe acute pancreatitis: A systematic review and meta-analysis. *Br J Nutr* 2014;112:1769-78
43. **Wu XM, Liao YW, Wang HY, et al. –** When to initialize enteral nutrition in patients with severe acute pancreatitis?: A retrospective review in a single institution experience (2003-2013). *Pancreas* 2015;44:507-11

44. **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;371:1983-93
45. **Zhao XL, Zhu SF, Xue GJ, et al. –** Early oral refeeding based on hunger in moderate and severe acute pancreatitis: A prospective controlled, randomized clinical trial. *Nutrition* 2015;31:171-5
46. **Besselink MG, van Santvoort HC, Buskens E, et al. –** Probiotic prophylaxis in predicted severe acute pancreatitis: A randomised, double-blind, placebo-controlled trial. *Lancet* 2008;371:651-9
47. **Click B, Ketchum AM, Turner R, et al. –** The role of apheresis in hypertriglyceridemia-induced acute pancreatitis: A systematic review. *Pancreatology* 2015;15:313-20
48. **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
49. **Maple JT, Ben-Menachem T, Anderson MA, et al. –** The role of endoscopy in the evaluation of suspected choledocholithiasis. *Gastrointest Endosc* 2010;71:1-9
50. **Neoptolemos JP, Carr-Locke DL, London NJ, et al. –** Controlled trial of urgent endoscopic retrograde cholangiopancreatography and endoscopic sphincterotomy versus conservative treatment for acute pancreatitis due to gallstones. *Lancet* 1988;2:979-83
51. **Fan ST, Lai EC, Mok FP, et al. –** Early treatment of acute biliary pancreatitis by endoscopic papillotomy. *N Engl J Med* 1993;328:228-32
52. **Folsch UR, Nitsche R, Ludtke 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;336:237-42
53. **Oria A, Cimmino D, Ocampo C, et al. –** Early endoscopic intervention versus early conservative management in patients with acute gallstone pancreatitis and biliopancreatic obstruction: A randomized clinical trial. *Ann Surg* 2007;245:10-7
54. **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
55. **Nebiker CA, Frey DM, Hamel CT, et al. –** Early versus delayed cholecystectomy in patients with biliary acute pancreatitis. *Surgery* 2009;145:260-4
56. **Overby DW, Apelgren KN, Richardson W, et al. –** SAGES guidelines for the clinical application of laparoscopic biliary tract surgery. *Surg Endosc* 2010;24:2368-86
57. **Falor AE, de Virgilio C, Stabile BE, et al. –** Early laparoscopic cholecystectomy for mild gallstone pancreatitis: Time for a paradigm shift. *Arch Surg* 2012;147:1031-5
58. **Aboulian A, Chan T, Yaghoubian A, et al. –** Early cholecystectomy safely decreases hospital stay in patients with mild gallstone pancreatitis: A randomized prospective study. *Ann Surg* 2010;251:615-9
59. **Bouwense SA, Bakker OJ, van Santvoort HC, et al. –** Safety of cholecystectomy in the first 48 hours after admission for gallstone pancreatitis not yet proven. *Ann Surg* 2011;253:1053-5
60. **Petrov MS, Windsor JA –** Very early cholecystectomy in patients with predicted mild acute pancreatitis: Caution advised. *Ann Surg* 2011;253:1051-5
61. **Nealon WH, Bawduniak J, Walser EM –** Appropriate timing of cholecystectomy in patients who present with moderate to severe gallstone-associated acute pancreatitis with peripancreatic fluid collections. *Ann Surg* 2004;239:741-51
62. **Mier J, Leon EL, Castillo A, et al. –** Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg* 1997;173:71-5
63. **Kirkpatrick AW, Roberts DJ, De Waele J, et al. –** Intra-abdominal hypertension and the abdominal compartment syndrome: Updated consensus definitions and clinical practice guidelines from the world society of the abdominal compartment syndrome. *Intensive Care Med* 2013;39:1190-206.