

## AGA SECTION

## American Gastroenterological Association Institute Guideline on Initial Management of Acute Pancreatitis



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This document presents the official recommendations of the American Gastroenterological Association (AGA) on the initial management of acute pancreatitis (AP). The guideline was developed by the AGA's Clinical Practice Guideline Committee and approved by the AGA Governing Board. It is accompanied by a technical review that is a compilation of the clinical evidence from which these recommendations were formulated.<sup>1</sup>

AP is an inflammatory condition of the pancreas that can cause local injury, systemic inflammatory response syndrome, and organ failure. Worldwide, AP is a common gastrointestinal condition that is associated with substantial suffering, morbidity, and cost to the health care system. In the United States, AP is a leading cause of inpatient care among gastrointestinal conditions: >275,000 patients are hospitalized for AP annually, at an aggregate cost of >\$2.6 billion per year.<sup>2</sup> The incidence of AP ranges from 5 to 30 cases per 100,000, and there is evidence that the incidence has been rising in recent years.<sup>3–5</sup> The overall case fatality rate for AP is roughly 5%, and is expectedly higher for more severe disease.<sup>6</sup> Patients with AP frequently experience abdominal pain, nausea, and vomiting, and the condition negatively impacts quality of life.<sup>7</sup> The most common causes of AP remain gallstones and alcohol, which together comprise 80% of cases; the remainder of cases are due to less common causes, including drug reactions, pancreatic solid and cystic malignancies, and hypertriglyceridemia.<sup>8</sup>

The diagnosis of AP requires at least 2 of the following features: characteristic abdominal pain; biochemical evidence of pancreatitis (ie, amylase or lipase elevated >3 times the upper limit of normal); and/or radiographic evidence of pancreatitis on cross-sectional imaging.<sup>9</sup> Presentations of AP occur along a clinical spectrum, and can be categorized as mild, moderately severe, or severe, based on the recent revised Atlanta classification.<sup>9</sup> Most cases of AP (around 80%)<sup>10</sup> are mild, with only interstitial changes of the pancreas without local or systemic complications. Moderately severe pancreatitis is characterized by transient local or systemic complications or transient organ failure (<48 hours), and severe AP is associated with persistent organ failure.<sup>9</sup> Necrotizing pancreatitis is characterized by the presence of pancreatic and/or peripancreatic necrosis, and is typically seen in patients with moderately severe or severe AP. Severity of disease factors into several of the

recommendations in this guideline. There are 2 overlapping phases of AP, early and late. The early phase of AP takes place in the first 2 weeks after disease onset, and the late phase can last weeks to months thereafter.<sup>9</sup>

In this guideline, we address the initial management of AP within the first 48–72 hours of admission. We focus on the initial management of AP, as this is the period when management decisions can alter the course of disease and duration of hospitalization. The management of AP has evolved slowly during the preceding 100 years. However, emerging evidence challenges many of the long-held management paradigms in AP regarding the benefit of antibiotics, the timing and mode of nutritional support, and the utility and timing of endoscopic retrograde cholangiopancreatography (ERCP) and cholecystectomy. Therefore, we sought to evaluate the sum of the evidence for these and other important questions regarding the management of AP.

Because of the focus on initial treatment of AP, certain questions pertaining to late complications of AP (eg, management of pancreatic fluid collections) are beyond the scope of this guideline. Additionally, because this guideline focuses on the management of AP, we will not address diagnostic questions, such as the use of laboratory tests or radiographic studies to establish the diagnosis of AP.

The guideline was developed utilizing a process outlined elsewhere.<sup>11</sup> Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology<sup>12</sup> and best practices as outlined by the Institute of Medicine.<sup>13</sup> GRADE methodology was utilized to prepare the background information for the guideline and the technical review that accompanies it.<sup>1</sup> Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. The guideline

**Abbreviations used in this paper:** AGA, American Gastroenterological Association; AP, acute pancreatitis; CI, confidence interval; ERCP, endoscopic retrograde cholangiopancreatography; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HES, hydroxyethyl starch; OR, odds ratio; RCT, randomized controlled trial.

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**Table 1.** Quality of Evidence Categories

Quality of evidence	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

panel and the authors of the technical review met face to face on July 18, 2017, to discuss the findings from the technical review. The guideline authors subsequently formulated the recommendations. Although the quality of the evidence (Table 1) was a key factor in determining the strength of the recommendations (Table 2), the panel also considered the balance between benefit and harm of interventions, patients' values and preferences, and resource utilization. The recommendations are summarized in Table 3.

**Recommendation 1A. In patients with AP, the AGA suggests using goal-directed therapy for fluid management. Conditional recommendation, very low quality evidence.**

*Comment: The AGA makes no recommendation whether normal saline or Ringer's lactate is used.*

Fluid therapy to prevent hypovolemia and organ hypoperfusion is a long-established cornerstone of the initial management of AP. However, the evidence basis for fluid therapy in AP is relatively weak. In the technical review, a total of 7 randomized trials were identified pertaining to fluid resuscitation, with 4 primarily addressing the role of goal-directed targeted therapy.<sup>1</sup> Goal-directed therapy is generally defined as the titration of intravenous fluids to specific clinical and biochemical targets of perfusion (eg, heart rate, mean arterial pressure, central venous pressure, urine output, blood urea nitrogen concentration, and hematocrit). Use of goal-directed therapy has been shown to lower mortality in sepsis,<sup>14</sup> a condition with physiologic similarities to AP. Compared to non-targeted therapy, goal-directed therapy did not result in significantly improved mortality, prevention of pancreatic necrosis, or decrease in the rate of persistent multiple organ failure. In this context, though there was not clear randomized controlled trial (RCT)—level evidence of benefit, the panel issued a conditional recommendation suggesting the use of judicious goal-directed fluid therapy vs other methods. However, the panel recognized that overly aggressive fluid therapy can be associated with harms in AP, including respiratory complications and abdominal compartment syndrome.<sup>15,16</sup> The overall quality of the evidence was very low due to the inconsistency among reported outcome measures (especially the lack of differentiation between transient and persistent organ failure), the small number of RCTs, outcome assessment (detection bias), and lack of blinding (performance bias). The lack of RCT evidence addressing the optimal initial rate, volume, and duration of fluid resuscitation in AP rendered the panel unable to make specific recommendations in this regard.

Regarding the use of Ringer's lactate vs normal saline as the optimal fluid solution for resuscitation, the panel could not make a recommendation based on the low quality of evidence. The 2 RCTs specifically addressing this topic used surrogate markers of severity and did not focus on

**Table 2.** Interpretation of Strength of Recommendation Categories

Strength of recommendation	Wording in the guideline	For the patient	For the clinician
Strong	"The AGA recommends..."	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	"The AGA suggests..."	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may be useful in helping individuals in making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.
No recommendation	"The AGA makes no recommendation..."		The confidence in the effect estimate is so low that any recommendation is speculative at this time

**Table 3.** Summary of Recommendations of the American Gastroenterological Association Clinical Guidelines for the Initial Management of Acute Pancreatitis

Recommendation	Strength of recommendation	Quality of evidence
1A. In patients with AP, the AGA suggests using goal-directed therapy for fluid management. <i>Comment: The AGA makes no recommendation whether normal saline or Ringer's lactate is used.</i>	Conditional	Very low
1B. In patients with AP, the AGA suggests against the use of HES fluids.	Conditional	Very low
2. In patients with predicted severe AP and necrotizing AP, the AGA suggests against the use of prophylactic antibiotics.	Conditional	Low
3. In patients with acute biliary pancreatitis and no cholangitis, the AGA suggests against the routine use of urgent ERCP.	Conditional	Low
4. In patients with AP, the AGA recommends early (within 24 h) oral feeding as tolerated, rather than keeping the patient nil per os.	Strong	Moderate
5. In patients with AP and inability to feed orally, the AGA recommends enteral rather than parenteral nutrition.	Strong	Moderate
6. In patients with predicted severe or necrotizing pancreatitis requiring enteral tube feeding, the AGA suggest either NG or NJ route.	Conditional	Low
7. In patients with acute biliary pancreatitis, the AGA recommends cholecystectomy during the initial admission rather than after discharge.	Strong	Moderate
8. In patients with acute alcoholic pancreatitis, the AGA recommends brief alcohol intervention during admission	Strong	Moderate

NG, nasogastric; NJ, nasojejunal.

important clinical outcomes, such as organ failure, necrosis, or mortality. The panel recognizes that the current intensive study of this topic may lead to changing this recommendation in the near future.

**Recommendation 1B. In patients with AP, the AGA suggests against the use of hydroxyethyl starch (HES) fluids. Conditional recommendation, very low quality evidence.**

The technical review revealed few studies that specifically addressed the issue of using HES as a resuscitative fluid in AP.<sup>1</sup> The panel's conditional recommendation against using HES fluids is based on 2 studies examining this issue,<sup>17,18</sup> with mortality not improved compared to fluid resuscitation without HES. Importantly, multiple organ failure was significantly increased in 1 trial with HES fluids (odds ratio [OR], 3.86; 95% confidence interval [CI], 1.24–12.04).<sup>18</sup> Unfortunately, other important outcomes, such as development of necrosis and/or persistent organ failure were not evaluated in these studies. These findings in AP mirror recent studies in the critical care literature, which have not demonstrated a mortality benefit of HES-containing fluids as resuscitative agents.<sup>19</sup>

**Recommendation 2. In patients with predicted severe AP and necrotizing pancreatitis, the AGA suggests against the use of prophylactic antibiotics. Conditional recommendation, low quality evidence.**

The technical review,<sup>1</sup> which included 10 RCTs addressing the role of prophylactic antibiotics in patients with predicted severe AP and necrotizing pancreatitis, demonstrated a reduction in the risk of infected pancreatic and peripancreatic necrosis (OR, 0.56; 95% CI, 0.36–0.86)

and a trend toward reduction in mortality (OR, 0.66; 95% CI, 0.42–1.04). However, in a subgroup analysis that included only recent trials published after 2002, no differences in risks of infected pancreatic and peripancreatic necrosis (OR, 0.81; 95% CI, 0.44–1.49) or mortality (OR, 0.85; 95% CI, 0.52–1.8) were noted. Similarly, there were no differences in these 2 critical outcomes among higher-quality studies. Given the higher methodologic quality of the recent studies, the guideline panel placed greater emphasis on results published after 2002 for this recommendation. Prophylactic antibiotics had no impact on the rates of important outcomes, such as persistent single organ failure, multiple organ failure or multiple organ dysfunction of unclear duration, single organ failure of unclear duration, and hospital length of stay. Though this recommendation statement is specific for patients with severe AP, it should be clarified that there is also no role for prophylactic antibiotics in patients with milder forms of AP. The overall quality of evidence was graded as low because of methodologic limitations (ie, risk of bias due to lack of blinding of participants and study personnel and imprecision).

**Recommendation 3. In patients with acute biliary pancreatitis and no cholangitis, the AGA suggests against the routine use of urgent ERCP. Conditional recommendation, low quality evidence.**

A total of 8 RCTs addressed the role of urgent ERCP in the management of patients with acute gallstone pancreatitis.<sup>1</sup> Compared to conservative management, urgent ERCP had no impact on critical outcomes, such as mortality and multiple organ failure, and on important outcomes, such as single organ failure (eg, respiratory or renal), infected pancreatic and peripancreatic necrosis, and total rates of necrotizing pancreatitis. Similar findings were noted in a

subgroup analysis of studies that clearly excluded patients with biliary obstruction. The guideline panel acknowledged the results of a single study demonstrating a reduction in hospital length of stay, but the overall body of evidence for this end point is sparse. The overall quality of evidence was graded as low given the inconsistency of results, indirectness of the evidence, and imprecision of results. The panel also acknowledged the limitations of published studies in excluding patients with acute cholangitis (a clear indication for ERCP in patients with or without acute biliary pancreatitis).

**Recommendation 4. In patients with AP, the AGA recommends early (within 24 hours) oral feeding as tolerated rather than keeping the patient nil per os. Strong recommendation; moderate quality evidence.**

Traditional dogma regarding management of AP prescribed “bowel rest” in an attempt to avoid further stimulation of the inflamed pancreas. However, current evidence demonstrates the benefit of the opposite approach, that is, early feeding. Maintaining enteral nutrition is thought to help protect the gut–mucosal barrier and reduce bacterial translocation, thereby reducing the risk of infected peripancreatic necrosis and other serious AP outcomes.<sup>20</sup>

Combined results of 11 RCTs that addressed the role of early vs delayed feeding demonstrated no difference in mortality for early vs delayed feeding. There was, however, a 2.5-fold higher risk of interventions for necrosis associated with delayed vs early feeding (OR, 2.47; 95% CI, 1.41–4.35), as well as trends observed for higher rates of infected peripancreatic necrosis (OR, 2.69; 95% CI, 0.80–3.60), multiple organ failure (OR, 2.00; 95% CI, 0.49–8.22), and total necrotizing pancreatitis (OR, 1.84; 95% CI, 0.88–3.86) associated with delayed feeding. Based on these studies, the AGA recommends initiation of early oral feeding (generally within 24 hours) instead of keeping patients NPO. While type of diet was not specifically examined in the technical review, success of early feeding has been demonstrated using a variety of diets including low-fat, normal fat, and soft or solid consistency,<sup>21</sup> and thus starting with a clear liquid diet is not required. The panel recognized that early feeding is not successful in all AP patients due to pain, vomiting, or ileus, and feeding may need to be delayed beyond 24 hours in some cases. Furthermore, some patients who are intolerant of oral feeding may require placement of an enteral tube for nutritional support (see Recommendations 5 and 6). However, routine or empiric orders for nil per os status in patients with AP should generally be avoided in favor of feeding trials. This is a strong recommendation based on the moderate quality evidence underpinning the statement.

**Recommendation 5. In patients with AP and inability to feed orally, the AGA recommends enteral rather than parenteral nutrition. Strong recommendation, moderate quality evidence.**

The technical review identified 12 RCTs that compared the use of parenteral (ie, total parenteral nutrition) vs enteral (oral or enteral tube) feeding in patients with AP. There was clear evidence to support the benefit of enteral nutrition over total parenteral nutrition with respect to reduced risk of infected peripancreatic necrosis (OR, 0.28; 95% CI, 0.15–0.51), single organ failure (OR, 0.25; 95% CI, 0.10–0.62), and multiple organ failure (OR, 0.41; 95% CI, 0.27–0.63). The AGA issued a strong recommendation based on the overall moderate quality of available evidence, and the likelihood of increased harm associated with the unnecessary use of parenteral nutrition.

**Recommendation 6. In patients with predicted severe or necrotizing pancreatitis requiring enteral tube feeding, the AGA suggests either nasogastric or nasoenteral route. Conditional recommendation, low quality evidence.**

Three RCTs were identified in the technical review that specifically addressed the issue of nasogastric vs nasoenteral (either nasoduodenal or nasojejunal) feeding in AP.<sup>1</sup> The trials did not demonstrate a mortality benefit associated with either modality (OR, 1.01; 95% CI, 0.44–2.30), but there were several methodologic issues that made the evidence of low quality, including a small number of RCTs, high risk of performance bias due to participant blinding, and a high risk of detection bias due to issues with outcome assessment. The studies also did not adequately address the issue of safety, including aspiration risk, with either of these modalities. The panel recognizes that safety concerns regarding the risk of aspiration may preclude practitioners from using nasogastric tubes in patients with severe AP.

**Recommendation 7. In patients with acute biliary pancreatitis, the AGA recommends cholecystectomy during the initial admission rather than after discharge. Strong recommendation, moderate quality evidence.**

Cholecystectomy can clearly prevent recurrent episodes of AP after an index case of biliary or gallstone pancreatitis.<sup>22</sup> However, the appropriate timing of cholecystectomy in patients with biliary or gallstone pancreatitis has been the subject of vigorous debate. The primary argument in favor of earlier intervention is that patients with biliary pancreatitis who are discharged without a cholecystectomy have a significant risk of recurrent biliary events.<sup>23</sup> However, those who advocate delayed cholecystectomy argue that performing surgery at a later time point when the acute inflammatory state of AP has subsided may be safer and associated with better surgical outcomes.

Moderate quality evidence from a single randomized controlled clinical trial<sup>24</sup> found that cholecystectomy performed during the initial admission for patients with suspected biliary pancreatitis was associated with substantial reductions in a composite outcome of mortality and gallstone-related complications (OR, 0.24; 95% CI, 0.09–0.61), readmission for recurrent pancreatitis (OR,



0.25; 95% CI, 0.07–0.90), and pancreaticobiliary complications (OR, 0.24; 95% CI, 0.09–0.61). Same-admission cholecystectomy did not differ from delayed cholecystectomy with respect to rates of conversion from laparoscopy to open approach or surgical difficulty. The AGA issued a strong recommendation due to the quality of available evidence and the high likelihood of benefit from early vs delayed cholecystectomy in this patient population.

**Recommendation 8. In patients with acute alcoholic pancreatitis, the AGA recommends brief alcohol intervention during admission. Strong recommendation, moderate quality evidence.**

The technical review identified significant knowledge gaps in this field with a paucity of RCTs addressing the role of alcohol counseling.<sup>1</sup> The panel's decision to provide a strong recommendation for a brief alcohol counseling intervention during admission was driven by the following published studies. A single RCT addressed the role of alcohol counseling on recurrent attacks of AP in patients with a first attack of AP with a clear history of alcohol use and exclusion of other possible etiologies.<sup>25</sup> Patients were randomized to either repeated intervention at 6-month intervals for 2 years at an outpatient gastrointestinal clinic or single intervention at initial hospitalization. There was a strong trend toward a reduction for total hospital admission rates with no statistically significant differences for outcomes, such as second attack of pancreatitis, definite recurrent pancreatitis, or  $\geq 2$  recurrent attacks of pancreatitis. The second source of evidence that supports this recommendation was a Cochrane review of alcohol reduction strategies in primary care populations (21 RCTs,  $n = 7286$ ), although not specifically addressing patients with AP.<sup>26</sup> This study showed that individuals receiving a brief intervention reduced alcohol consumption compared to the control group (mean difference:  $-41$  g/wk; 95% CI,  $-57$  to  $-25$  g/wk), with substantial heterogeneity in results. Extended intervention compared to brief intervention was associated with a nonsignificantly greater reduction in alcohol consumption. Finally, A follow-up meta-analysis addressing the effectiveness of brief interventions in primary care and differences between efficacy and effectiveness trials demonstrated similar results in reduction in alcohol consumption in participants receiving a brief intervention and no significant difference in effect sizes for efficacy and effectiveness trials.<sup>27</sup> The overall evidence for this recommendation was graded down to moderate, given the indirectness of evidence, risk of bias associated with lack of blinding, and imprecision of results.

## Summary

These practice guideline recommendations for the initial management of AP were developed using the GRADE framework and in adherence with the standards for guideline development set forth by the Institute of Medicine for the creation of trustworthy guidelines.<sup>11,13</sup> These guidelines are intended to reduce practice variation and promote

high-quality and high-value care for patients with AP. Current evidence supports the benefit of goal-directed fluid resuscitation, early oral feeding, and enteral rather than parenteral nutrition, in all patients with AP. Our evidence profiles also support the benefit of same-admission cholecystectomy for patients with biliary pancreatitis, and brief alcohol intervention for patients with alcohol-induced pancreatitis. In contrast, current evidence does not support a benefit for the routine use of prophylactic antibiotics in predicted severe AP or routine ERCP in patients with AP without accompanying cholangitis.

There are several knowledge gaps in the initial management of AP that have been identified for which RCTs are warranted, as is highlighted in the technical review that accompanies this guideline.<sup>1</sup> More evidence is needed to determine the optimal fluid therapy practice in AP, and to better quantify the benefits and harms of goal-directed therapy vs other approaches. Current evidence does not support a clear benefit of Ringer's lactate solution compared to normal saline for important outcomes, such as organ failure, necrosis, or mortality. Future RCTs addressing this topic would provide helpful guidance in this regard. Though risk stratification of patients with AP is important to ensure appropriate level of care, there is a dearth of high-quality evidence measuring the actual clinical impacts of using any particular severity prediction tool. High-quality multicenter RCTs are required to determine whether prophylactic antibiotics have a role in specific groups of patients with predicted severe AP and necrotizing pancreatitis. The appropriate timing of ERCP in patients with predicted severe biliary pancreatitis with persistent biliary obstruction also needs to be clarified in future studies. In addition, future research should focus on the impact of alcohol and tobacco cessation interventions on end points, such as recurrent AP, progression to chronic pancreatitis and pancreatic cancer, quality of life, health care utilization, and mortality.

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#### Conflicts of interest

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