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Initial Medical Treatment of Acute Pancreatitis: American Gastroenterological Association Institute Technical Review

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Acute pancreatitis (AP) was the third most common gastrointestinal diagnosis in 2012, resulting in approximately 275,000 admissions and costing about $2.6 billion.[1,2] It is also the most common pancreatic disease worldwide.[3] The incidence is increasing, but death rates have actually decreased in recent years to <2%.[1] However, ≥50% of the deaths occur within the first 2 weeks of diagnosis.[4,5] The recent revised Atlanta classification[6] described mild (usually interstitial), moderately severe (local complications without persistent organ failure), and severe (persistent organ failure) AP subtypes. Necrotizing pancreatitis is defined by the presence of pancreatic and/or peripancreatic necrosis and is usually associated with moderately severe or severe subtypes. Mild or interstitial AP is the most common type observed in 75%−80% of all patients. A fourth class of severity, critical AP, is described in the determinant-based classification[7] when both infected necrosis and persistent organ failure are present together.

AP has 2 phases, each with hallmark clinical features. The early phase spans the first 1−2 weeks and the late phase begins at 2 weeks and beyond. Whereas the systemic inflammatory response syndrome (SIRS) and the resultant organ failure dominate the early phase, the late phase is characterized by local complications of necrosis and pancreatic fluid collections, including infection, which is much more common in the late phase.[6]

To date, there is no drug available to treat AP, so most care is supportive. With this limitation, most clinical management guidelines[8,9] emphasize an approach that includes predicting and establishing the severity of AP to triage patients to appropriate levels of care; administering supportive care, including intravenous hydration and enteral nutrition; and treating the underlying cause and complications by appropriate use of urgent endoscopic retrograde cholangiopancreatography (ERCP), early cholecystectomy, targeted use of antibiotics, and interventions for pancreatic fluid collections in the later stages, usually after 4 weeks.

There is general agreement that the "initial period" of AP refers to the first 72 hours after diagnosis (the median length of stay for all patients is 3 days).[1] Key management in this phase includes identifying the cause, predicting the severity, intravenous hydration, and urgent ERCP (if indicated). Other treatment decisions, for example, enteral nutrition, early cholecystectomy, and alcohol counseling before hospital discharge, may take place beyond the first 72 hours, which might support extending the "initial period" of management up to 7 days after diagnosis. For the purpose of this technical review, the initial period encompasses the first 7 days, although most of the discussion pertains to the initial 72 hours. This review does not address imaging because it is not necessary to obtain a computed tomography scan early on if 2 criteria (typical pain and ≥3-fold elevation of pancreatic enzymes) are present. Also the need for magnetic resonance imaging, endoscopic ultrasound, and repeat computed tomography scan, if one is performed initially, are all beyond the scope of this review. There is unanimity about routine use of abdominal ultrasound to detect gallstones and sludge (observed in approximately 30%−40% of all cases of AP).[8,9]

Despite several observational and randomized trials, and an abundance of guidelines, systematic reviews, and meta analyses, many management decisions in AP are far from clear, including the optimal method of intravenous hydration; ideal predictor of severity; timing of oral feeding; type of initial oral food; indication, timing, and method of enteral nutrition; role of prophylactic antibiotics; role of urgent ERCP; timing of cholecystectomy in biliary AP; and interventions before admission for alcohol cessation for alcoholic AP.

This led the American Gastroenterological Association (AGA) Institute to undertake a technical review of the initial medical treatments for AP, specifically those that impact outcomes.[10] The main purpose is to critically review studies using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology and to generate summary evidence and estimates for the guidelines panel to develop evidence-based recommendations.[11–24]

Abbreviations used in this paper: **AGA, American Gastroenterological Association; AP, acute pancreatitis; BUN, blood urea nitrogen; CI, confidence interval; CRP, C-reactive protein; ERCP, endoscopic retrograde cholangiopancreatography; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HES, hydroxyethyl starch; LOS, length of stay; MOF, multiple organ failure; NG, nasogastric; NJ, nasojejunal; npo, nil per os; OR, odds ratio; PICO, population, intervention, comparator, and outcome; PMOF, persistent multiple organ failure; PSOF, persistent single organ failure; RCT, randomized controlled trial; SIRS, systemic inflammatory response syndrome; TPN, total parenteral nutrition; WMD, weighted mean difference.**

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Methods

Overview

This review collects and evaluates pertinent literature concerning the acute early management (first 72 hours, up to 7 days for certain treatments) of patients presenting with AP, focusing on therapeutic interventions that impact outcomes. With these data, the AGA's Medical Position Panel will, in turn, produce the final set of recommendations, as described previously.[10] Methods for deriving focused clinical questions, systematically reviewing and rating the quality of evidence for each outcome, and rating the overall quality of evidence were based on the GRADE framework, which have been described in detail elsewhere,[11–24] and are more specifically reported here.

The PICO format frames a clinical question by defining a specific patient population (P), intervention (I), comparator (C), and outcome(s).

Formulation of Clinical Questions

The participants included SSV, CEF, MJD, and ANB as selected by the AGA Clinical Guidelines Committee based upon clinical content and guidelines methodologic expertise. Focused questions were generated, and for each question a statement was framed in terms of a respective PICO.[25] In accordance with a modified Delphi method, the questions and PICO statements were developed by multiple structured iterations until a consensus among experts was reached.[26,27] The final proposed clinically pertinent list of topics addressed focused on questions and PICO statements related to the early management of patients presenting with AP. The AGA Governing Board approved the final set of questions. The final PICO statements are shown in Supplementary Table 1.

Search Strategy

An experienced librarian conducted distinct computer medical literature searches using the following databases until February 2016: Medline, Embase, Cochrane, and Health Technology Assessment. All searches included a highly sensitive search strategy to identify reports of randomized trials with a combination of controlled vocabulary and text words; the patient population targeted was those presenting with AP. With regard to interventions, the first search performed for PICO question 1 included the terms related to aggressive hydration. PICO question 2 included terms related to antibiotic prophylaxis. PICO question 3 included terms for ERCP, biliary tract diseases, and gallstones. The searches for PICO questions 4, 5, and 6 were combined and included terms related to nutrition support, artificial feeding, and dietary supplements or type. PICO question 7 included terms related to cholecystectomy. PICO question 8 included terms related to alcohol-related disorders or counseling (complete search strings are shown in Supplementary Table 2). The search for PICO question 9 were related to disease severity or scoring systems. In addition, recursive searches and cross-referencing were performed, and hand searches of articles identified after the initial search were also completed.

Trial Selection and Patient Population

Only fully randomized controlled trials (RCTs) published in English during the prespecified time periods were included (see search strings, Supplementary Table 2). Studies comprising pediatric populations, as well as Letters, Notes, Case Reports, or Comments, and any trials published in languages other than English were excluded.

Choice of Outcomes

Lists of prespecified critical and important outcomes were identified a priori. Although most were common to all PICOs, certain additionally clinically relevant outcomes pertinent to some questions were also specified. Death, single or multiple persistent organ failure (>48 hours), and infected pancreatic and/or peripancreatic necrosis are the clinical outcomes of importance in AP.[28] Hospital stay, need for and length of intensive care unit stay, and need for interventions are surrogate markers for the important clinical outcomes mentioned here,[29] but are commonly reported in most of the studies along with transient organ failure, which does not qualify to make the diagnosis of severe acute pancreatitis (SAP). A list of all outcomes with their respective ordinal ranking is shown in Supplementary Table 3. Blank cells indicate an outcome that was sought but not reported in selected studies.

Validity Assessment

Three investigators (SSV, CEF, and MJD) evaluated study eligibility independently, with discrepancies resolved after discussion and reaching a consensus. Data extraction was thoroughly performed by content experts (SSV, CEF, and MJD). Risk of bias for individual studies was assessed using the Cochrane Risk of Bias Tool. The quality of the evidence for each outcome and overall for each PICO was rated as very low, low, moderate, or high, based on the GRADE methodology[30]; disagreements were resolved by discussion. Quality of evidence definitions are available elsewhere.[30]

Statistical Methods

For each outcome and in every comparison, effect size was calculated as odds ratios (ORs) for categorical variables and weighted mean differences (WMDs) for continuous variables, where applicable. The DerSimonian and Laird method[31] for random effect models was applied to determine corresponding overall effect sizes and their confidence intervals (CIs), as the population was thought to include heterogeneous population or methods across the included trials. WMDs were handled as continuous variables using the inverse variance approach. The presence of statistical heterogeneity across studies was defined using a χ^2 test of homogeneity with a 0.10 significance level. The Higgins I^2 statistic was calculated to quantify the proportion of variation in treatment effects attributable to between-study heterogeneity[32]; values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively.

Values for intention-to-treat were preferred to per protocol when both were presented. Depending on what data were available or could be reconstructed, in order to minimize bias, we included noncompliant patients or withdrawals in the intention-to-treat analysis.[33] For all comparisons, publication bias was evaluated using funnel plot asymmetry[34] (data available upon request). All percentages of outcomes reported in the trials were converted to absolute numbers and no attempt at determining extractable values from graphics or figures was made to avoid any subjective interpretation. All statistical

analyses were completed using Review Manager (RevMan), version 5.3 (The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) and Meta package in R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria, 2008).

Presentation of Results

We present each focused question related to one of the PICO statements and the grading of the evidence for each component of the statement. After pertinent background information, the quantitative results are then presented along with pertinent narrative information to provide explanatory context for the results; the evidence base reports detail the rationale for the grading of quality of evidence. Suggested future research is also identified. Related PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagrams are presented in Supplementary Material 4 and Cochrane Risk of bias tool assessments in Supplementary Material 5. Related Forest plots are available upon request.

Results

Question 1: What is the Role of Intravenous Hydration in the Initial Management of Patients With Acute Pancreatitis?

Effect of fluid resuscitation on the outcomes of mortality, infected pancreatic necrosis, persistent multiple organ failure (PMOF), persistent single organ failure (PSOF), multiple organ failure (MOF) of unclear duration, single organ failure (unclear duration) and hospital length of stay (LOS).

Quality of evidence: Very low

Background information. Many different hydration solutions and methods of administration have been studied in the initial management of AP. Hypovolemia in AP can occur for many reasons, including third-space fluid loss.[35] Hypovolemia contributes to renal and circulatory failure and also can lead to or exacerbate a microcirculatory defect in the pancreas, resulting in worse pancreatic and peripancreatic necrosis.[36] Thus, the rationale of fluid therapy in the initial management of AP has been emphasized in all guidelines to prevent these consequences. Although limited in number, randomized trials have assessed the role of crystalloid solutions, colloid expanders, and, more recently, goal-directed therapy. The various aims and metrics of goal-directed therapy include heart rate, blood pressure, mean arterial pressure, urine output, hematocrit, blood urea nitrogen (BUN), creatinine, central venous pressure, stroke volume variation, and intrathoracic blood volume. Whereas goal-directed therapy had a specific definition when it was developed for treatment of sepsis,[37] it has also been studied in a breadth of conditions using heterogeneous goals and protocols, such that a recent systematic review[38] found scant high-quality evidence for the numerous goal/method combinations. In AP, 3 guidelines are instructive. Recommendations were weak[8] or strong[9,39] for lactated Ringer's solution as the preferred type of fluid, with different rates and levels of evidence: 5−10 mL/kg/h[9] (moderate quality evidence), 250−500 mL/h during the first 12−24 hours using frequent clinical assessments to decrease BUN[8] (moderate quality evidence), and 150−600 mL/h[39] (low-quality evidence). One guideline[9] also made weak recommendations for goal-directed therapy using clinical, biochemical, and invasive targets (moderate quality evidence). As a more sobering appraisal of the literature, the systematic review by Haydock et al[35] analyzed 15 studies (including 4 RCTs) and concluded that fluid therapy is considered a cornerstone of the early management of patients with AP and yet the evidence on which it is based remains "paltry and of poor quality."

Results from the current systematic review. From an initial 382 citations, 7 RCTs addressed different solutions or methods of administering intravenous fluids in the initial management of AP; experimental interventions in some studies were also considered a control fluid administration in others. These publications also report different outcomes in varying populations of patients with AP (Table 1).

Four trials (n = 431) examined predefined rapid hydration or gradual hydration. Mortality was not significantly different between groups (4 trials; OR, 1.92; 95% CI, 0.69−5.37) nor was infected pancreatic necrosis (1 trial, OR, 3.49; 95% CI, 0.13−90.86) or PMOF (1 trial, OR, 0.35; 95% CI, 0.01−9.13). None of the other critical outcomes sought where reported in the included trials. An additional trial by Sharma et al[40] assessed nasojejunal (NJ) goal-directed therapy compared to intravenous goal-directed therapy, but the data could not be analyzed with these studies because it compared 2 different goal-directed therapies. None of the reported critical outcomes differed between groups in this trial (Table 2).

While lactated Ringer's has the theoretical benefit of decreasing pancreatic acidosis and reducing trypsin activity, and has been shown to improve outcomes like C-reactive protein (CRP) levels and SIRS in some trials, treatment allocation and choice of outcomes did not allow for a determination of the impact of lactated Ringer's administration for any of the chosen critical or important outcomes.

In the 2 trials (n = 161) that examined the administration of 6% hydroxyethyl starch (HES, a non-ionic starch derivative used as a volume expander) compared to fluids without 6% HES, mortality was not significantly different (2 trials; OR, 0.47; 95% CI, 0.15−1.51). Rates of infected pancreatic necrosis, PMOF, and PSOF were not reported in the included trials. MOF was significantly increased (OR, 3.86; 95% CI, 1.24−12.04) with 6% HES administration in 1 trial[41] (Table 3).

An important limitation of this analysis is that most of the studies did not distinguish between transient and persistent organ failure because many predated the prognostically important new definition of persistent organ failure.[6] Hence, the single and multiple organ failure diagnoses in these studies included both transient and persistent types. The interpretation of these results is further limited by a serious risk of bias in many trials, the small number of studies, wide uncertainty around efficacy point estimates as reflected by broad CIs, and lack of consistency in outcome findings across different trials.

Even more pronounced methodologic limitations apply to the results addressing some of the a priori−defined

Table 1. Role of Intravenous Hydration: Included Trials

First author, year, country	Patient population	AP definition	Descriptor	Bolus	Maintenance	Crystalloids	Colloids	Crystalloid to colloid ratio	Other
Goal-directed therapy									
Mao, 2009[88] China	Inclusions: HR ≥120 beats/min, MAP ≥85 mm Hg or ≤60 mm, BLC ≥ 4 mmol/L, urine output ≤0.5 mL/kg/h, Hct ≥44%. Exclusions: age <18 y or >70 y, pregnancy, CHD, pacemaker, chronic renal failure, and SAP with uncertain etiology	None Severe per Atlanta 1992	Rapid hydration[a]	—	10–15 mL/kg/h	NS ± LR	6% HES + plasma	2:1	—
			Gradual hydration[b]	—	5–10 mL/kg/h	NS ± LR	6% HES + plasma	2:1	—
Mao, 2010[89] China	Inclusions: first AP attack within 24 h after onset symptoms, conscious, APACHE II >8, Hct ≥44% Exclusions: age <18 y or >70 y, pregnancy, CHD, pacemaker chronic renal failure and SAP with uncertain etiology	Conventional (Atlanta) definition: 2 of 3 (typical pain, >3× ULN enzymes and imaging)	Rapid hemodilution[a]	—	Rate estimated based on weight and admit/goal Hct	NS ± LR	6% HES + plasma	2:1	—
			Slow hemodilution[b]	—	Rate estimated based on weight and admit/goal Hct	NS ± LR	6% HES + plasma	2:1	—
Wu, 2011[42] USA	Inclusion: age ≥18 y, AP Exclusion: NYHA >2, myocardial ischemia, cardiovascular intervention, cirrhosis, chronic kidney disease with creatinine clearance <40 mL/min, COPD, hypo- or hypernatremia, rhabdomyolysis, IBD, autoimmune conditions, HIV, TB	Conventional (Atlanta) definition: 2 of 3 (typical pain, >3× ULN enzymes and imaging)	Goal-directed[a]	20 mL/kg	3 mL/kg/h	NS + LR	—	—	—
			Standard[b]	—	—	NS + LR	—	—	—

Table 1. Continued

First author, year, country	Patient population	AP definition	Descriptor	Bolus	Maintenance	Crystalloids	Colloids	Crystalloid to colloid ratio	Other
Wang et al. 2013[90] China	Inclusion: SAP defined by Atlanta Criteria and admitted to the ICU within 24 h after onset of disease Exclusion: age <18 y or >70 y, sepsis, pregnancy, CHD, pacemaker, chronic renal failure, SAP with unknown etiology	Conventional (Atlanta) definition: 2 of 3 (typical pain, >3× ULN enzymes and imaging)	Goal-directed[a]	—	Physiologic need	NS + LR	6% HES	2:1	—
			Goal-directed[a]	—	Physiologic need	NS + LR	6% HES + 2 U FFP	2:1	—
			Goal-directed[b]	—	Control (Banks)	NS + LR	6% HES	2:1	—
Sharma, 2016[40] India	Inclusion: Predicted SAP defined by SIRS ≥2 or BISAP >2 Exclusion: Presenting >5 d after onset pain; presenting with shock, CHF, history of myocardial ischemia, cirrhosis, CKD (CrCl ≤40 mL/min), COPD, concurrent metabolic or physiologic derangement that required specific fluid management like hypo- or hypernatremia, diabetic ketoacidosis; patients transferred from other hospital after initial treatment; suspicion of chronic pancreatitis; biliary pancreatitis needing ERCP for cholangitis, pregnancy; severe lung injury precluding endoscopy and NJ tube placement.	Conventional (Atlanta) definition: 2 of 3 (typical pain, >3× ULN enzymes and imaging)	NJ goal-directed[a]	20 mL/kg	3 mL/kg/h	—	—	—	WHO ORS
			IV goal-directed[b]	20 mL/kg	3 mL/kg/h	LR	—	—	—

Table 1. Continued

First author, year, country	Patient population	AP definition	Descriptor	Bolus	Maintenance	Crystalloids	Colloids	Crystalloid to colloid ratio	Other
Fluid type variation									
Du, 2011[91] China	Inclusion: SAP defined per 2002 World Congress of gastroenterology Guidelines and within 72 h of onset of symptoms Exclusion: allergy to starch, NYHA class 3 or 4, renal insufficiency, serum albumin <25 g/L, INR >3, possible mortality within 48 h, colloids in 24 h prior or participation in clinical drug research within 3 mo prior	None for AP. 2002 guidelines definition for SAP	LR + 6% HES[a]	—	1–2 mL/kg/h	NS + LR	6% HES	3:1	—
			LR only[b]	—	1–2 mL/kg/h	LR	—	—	—
Zhao, 2013[41] China	Inclusion: SAP per Atlanta criteria, age >18 y or <60 y, transfers Exclusion: heart disease, severe renal and hepatic dysfunction, coagulation disturbances, and allergy to starch or glutamine	Per Atlanta criteria for "SAP"—presumably 2/3 criteria per Atlanta paper	NS + 6% HES[a]	1L	2–3 mL/kg/h	NS	6% HES	3:1	—
			NS + 6% HES + glutamine[b]	1L	2–3 mL/kg/h	NS	6% HES	3:1	Glutamine supplement
			NS[b]	1L	2–3 mL/kg/h	NS	—	—	—

BISAP, Bedside Index for Severity in Acute Pancreatitis; BLC, blood lactate concentration; CHD, chronic heart disease; CHF, congestive hear failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance; FFP, fresh-frozen plasma; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; INR, international normalized ratio; NS, normal saline; NYHA, New York Heart Association; RL, Ringer's lactate; HR, heart rate; MAP, mean arterial pressure; Hct, hematocrit; ORS, oral rehydration solution; TB, tuberculosis; WHO, World Health Organization.
[a]Intervention arm.
[b]Control arm.

Table 2. Goal-Directed Therapy Compared to Control for Acute Pancreatitis: Grading the Evidence

Quality assessment							Patients, n (%)		Effect, OR (95% CI)			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Goal-directed therapy	Control	Relative	Absolute	Quality	Importance
Mortality, n = 4	Randomized trials	Serious[a]	Serious[b]	Not serious	Very serious[c]	None	56/243 (23.0)	29/188 (15.4)	1.92 (0.69–5.37)	105 more per 1000 (from 42 fewer to 341 more)	⊕○○○ Very low	Critical
PMOF or PMODS, n = 1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[c]	None	0/19 (0.0)	1/21 (4.8)	0.35 (0.01–9.13)	30 fewer per 1000 (from 47 fewer to 266 more)	⊕○○○ Very low	Critical
PSOF, NR	—	—	—	—	—	—	—	—	—	—	—	—
Total necrotizing pancreatitis, NR	—	—	—	—	—	—	—	—	—	—	—	—
Infected (peri) pancreatic necrosis, n = 1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[c]	None	1/19 (5.3)	0/21 (0.0)	3.49 (0.13–90.86)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕○○○ Very low	Important
MOF or MODS (unclear duration), n = 1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[c]	None	34/132 (25.8)	20/68 (29.4)	0.83 (0.43–1.60)	37 fewer per 1000 (from 106 more to 142 fewer)	⊕○○○ Very low	Important
SOF (unclear duration), NR	—	—	—	—	—	—	—	—	—	—	—	—

MOD, multiple organ dysfunction; NR, not reported; PMOD, persistent multiple organ dysfunction; SOF, single organ failure.
[a]High risk for 2 elements: blinding of participants and personnel and blinding of outcome assessment.
[b]Strong statistical heterogeneity.
[c]Optimal information size not meet, very small sample size.

Table 3. Fluids With 6% Hydroxyethyl Starch Compared to Fluids Without 6% Hydroxyethyl Starch for Acute Pancreatitis: Grading the Evidence

Quality assessment							Patients, n (%)		Effect, OR (95% CI)			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluids with 6% HES	Fluids without 6% HES	Relative	Absolute	Quality	Importance
Mortality, n = 2	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	6/100 (6.0)	7/61 (11.5)	0.47 (0.15−1.51)	57 fewer per 1000 (from 49 more to 96 fewer)	⊕○○○ Very low	Critical
PMOF or PMODS, NR	—	—	—	—	—	—	—	—	—	—	—	—
PSOF, NR	—	—	—	—	—	—	—	—	—	—	—	—
Total necrotizing pancreatitis, NR	—	—	—	—	—	—	—	—	—	—	—	—
Infected (peri) pancreatic necrosis, NR	—	—	—	—	—	—	—	—	—	—	—	—
MOF or MODS (unclear duration), n = 1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious[b]	None	24/80 (30.0)	4/40 (10.0)	3.86 (1.24−12.04)	200 more per 1000 (from 21 more to 472 more)	⊕○○○ Very low	Important
SOF (unclear duration), NR	—	—	—	—	—	—	—	—	—	—	—	—

NR, not reported; PMOD, persistent multiple organ dysfunction; SOF, single organ failure.
[a]High risk for 2 elements: blinding of participants and personnel and blinding of outcome assessment.
[b]Optimal information size not meet, very small sample size.

critical outcomes, with even fewer studies including extractable data for these (Table 1). As an example, the study by Wu et al[42] showed improved outcomes attributable to the use of a lactated Ringer's solution vs normal saline (for goal-directed and standard volume administration protocols grouped together for each fluid type) but only with regard to the incidence of SIRS after 24 hours (84% reduction vs 0%, respectively; $P = .035$), and reduced CRP levels (51.5 vs 104 mg/dL, respectively; $P = .02$).

In conclusion, there is insufficient evidence to state that goal-directed therapy, utilizing various parameters to guide fluid administration, reduces the risk of persistent single or multiple organ system failure, infected (peri) pancreatic necrosis or mortality from AP. There is also no RCT evidence that any particular type of fluid therapy (eg, lactated Ringer's) reduces the risk of mortality or persistent single or multiple organ failure. The addition of HES to usual intravenous fluids does not reduce the risk of mortality, and may increase the risk of persistent multiple organ system failure in AP.

Recommendations for future clinical trials on the topic. We would suggest that intravenous hydration in AP include the following goals: (1) enroll consecutive patients (because there is no reliable method at the present time to predict moderately severe or severe types); (2) prioritize the measurement of critical outcomes outlined in this systematic review; (3) and attempt to address important but unanswered questions, including the role of goal-directed therapy and the type of goal-directed therapy, the type of fluid to be used (lactated Ringer's, saline, synthetic colloids), as well as the volume and rate of fluid therapy, and its timing of administration as well as duration.

Question 2: What Is the Role of Prophylactic Antibiotics in Predicted Severe Acute Pancreatitis and Necrotizing Acute Pancreatitis?

Effect of prophylactic antibiotics on the outcomes of mortality, infected pancreatic necrosis, PMOF, PSOF, MOF, or multiple organ dysfunction of unclear duration, single organ failure of unclear duration, and hospital LOS.

Quality of evidence: Low

Background information. Infections in AP (pancreatic and extrapancreatic) are common and result in significant morbidity and mortality. While the original Atlanta classification[43] defined several local pancreatic complications (pseudocyst, necrosis, or abscess), which were classified as SAP, the revised Atlanta classification defined local complications as acute collections (acute peripancreatic and pancreatic fluid collections, acute necrotic collections) or mature collections (pseudocyst and walled-off necrosis), which were classified as moderately severe AP or SAP, respectively, depending on the absence or presence of persistent organ failure.[6] Necrotizing pancreatitis includes both peripancreatic and pancreatic necrotic collections, which mature into collections of walled-off necrosis, usually after 4 weeks. Infected necrosis is infection of (peri) pancreatic necrosis, and is associated with high mortality (in the range of 30%).[8] According to a recent systematic review, mortality doubles when (peri) pancreatic necrosis becomes infected in patients with coexisting organ failure.[44] Reducing infected necrosis, morbidity, and mortality is the rationale for administering prophylactic antibiotics (before a documented infection) to patients with either predicted SAP (which is associated with a higher risk of developing necrotizing pancreatitis) or those with established necrotizing pancreatitis. The antibiotics used in most of the AP trials were capable of penetrating the infected necrosis, for example, fluoroquinolones, metronidazole, carbapenems, and third-generation cephalosporins. Whereas earlier trials and meta-analyses often showed that prophylactic antibiotics improved certain outcomes (eg, mortality and infectious complications), more recent studies and meta-analyses have often failed to confirm such benefit, likely due to higher-quality methodology over time.[45,46] Inherent methodologic problems described by earlier reviews and recent meta-analysis are most pronounced among older studies and include differences in inclusion criteria, variable prophylactic antibiotic treatment regimens, inconsistent double blinding, and use of non-placebo controlled study design that compares 2 antibiotics. Hence, recent guidelines do not recommend prophylactic antibiotics to prevent infection in sterile necrosis in AP.[8,9] A persistent concern in the field is that methodologic problems across trials might mask detection of an important clinical benefit of prophylactic antibiotics, perhaps in certain subgroups with extensive necrosis[47] and persistent organ failure (usually known only after 48 hours).

Results of the current systematic review. From 263 citations, we identified 10 RCTs (n = 701) that addressed the role of prophylactic antibiotic coverage (Table 4). Mortality exhibited a trend toward reduction with the prophylactic use of antibiotics (OR, 0.66; 95% CI, 0.42−1.04) that disappeared in subgroup analysis among more recent studies (after 2002: OR, 0.85; 95% CI, 0.52−1.80) (Table 5). Infected peripancreatic necrosis, was significantly lowered with antibiotic prophylaxis (OR, 0.56; 95% CI, 0.36−0.86), but no difference in this outcome was noted among more recent trials (OR, 0.81; 95% CI, 0.44−1.49) (Table 5). Similarly, no between-group differences in mortality or peripancreatic necrosis were noted among higher-quality trials (data available upon request). Persistent single organ failure was not reduced by prophylaxis antibiotics (OR, 0.19; 95% CI, 0.01−4.06). No studies reported on the outcome of PMOF. None of the additional important outcomes were significantly improved with prophylactic antibiotic administration, including MOF or multiple organ dysfunction of unclear duration, single organ failure of unclear duration, and hospital LOS (Table 5).

The absence of significant findings among more recent and better-quality trials is likely attributable to the methodologic limitations mentioned, more prominently noted among older trials.

Several trials related to the focus of this AGA technical review were of interest but were excluded because the nature of the intervention was not sufficiently comparable to prophylactic intravenous antibiotic treatment trials

Table 4. Antibiotic Prophylaxis: Included Trials

First author, year, country	Patient population	AP definition	Nature	Dosage	Duration
Pederzoli, 1993[92] Italy	Inclusions: no previous pancreatic disease, admission within 48 h of onset of symptoms, availability of CE-CT within 72 h and detectable pancreatic necrosis. Exclusions: not specified	None	Imipenem[a]	2g IV every 8 h	2 wk
			Standard treatment[b]	—	Until hospital discharge
Luiten, 1995[93] Netherlands	Inclusions: SAP (defined by Imrie score ≥3 and/or CT Balthazar grade D or E Exclusions: Allergy to one of antibiotics; age <18 y; postoperative pancreatitis after pancreatic surgery; bacteriologically proven infected necrosis at the time of randomization	Clinical symptoms and either amylase >1000 IU or laparotomy findings (10 patients)	Selective gut contamination with norfloxacin, colistin, amphotericin[a]	Colistin sulfate: oral 200 mg q6h; 2% paste gums q6h and enema qd Oral amphotericin 500 mg q6h; 2% paste gums q6h and enema qd Oral norfloxacin 50 mg q6h; 2% paste gums q6h and enema qd Cefotaxime 500 mg IV q8h (until GN bacterial eliminated from oral cavity and rectum)	Until patient extubated and without supplemental oxygen, on regular diet, and out of ICU (time on therapy not reported)
			Placebo (actually no placebo given, just standard care)[b]		
Delcenserie, 1996[94] France	Inclusions: No previous pancreatic disease, admission within 48 h of onset of symptoms, no previous antibiotics, acute alcoholic pancreatitis with 2 or more fluid collections on CT Exclusions: not specified	Not mentioned	Ceftazidine, metronidazole, amikacin, and medical treatment[a]	2 g q8h, 0.5 g q8h, 7.5 mg/kg body weight every 12 h	10 d
			Medical treatment alone[b]		During hospitalization
Sainio, 1995[95] Finland	Inclusions: etiology due to alcohol, SAP with pancreatic necrosis (low enhancement on CE-CT) and CRP >12 mg/L within 48 h of admission. If CE-CT contraindicated (renal insufficiency, contrast allergy) patients could be enrolled for having "early extrapancreatic scores" ≥4 points Exclusions: Treatment elsewhere for >2 d before admission to Helsinki University Central Hospital, continuing antimicrobial treatment, previous SAP, etiology other than alcohol, no history of alcohol intake before admission	Conventional (Atlanta) definition: 2 of 3 (typical pain, >3× ULN enzymes and imaging)	IV cefuroxime[a]	4.5 g/d	Unclear
			No antibiotic[b]		Until clinical or microbiologically verified infection or after secondary rise in CRP

Table 4. Continued

First author, year, country	Patient population	AP definition	Nature	Dosage	Duration
Nordback, 2001[96] Finland	Inclusions: AP (3 of 3), elevated CRP > 150 mg/L, CT evidence of necrosis (<30 HU) Exclusions: Age > 70 y, previously received antibiotics, MOF at presentation, allergy to drug	Conventional (Atlanta) definition: 2 of 3 (typical pain, >3× ULN enzymes and imaging)	Imipenem starting within 48 h of onset[a]	1 g tid	NS until patient was a febrile and WBC normalized
			Imipenem if criteria of infection met[b]	1 g tid	NS until patient was afebrile and WBC normalized
Isenmann, 2004[97] Germany	Inclusions: CRP > 150 mg/100 mL and/or pancreatic necrosis on CE-CT scan Exclusions: not reported	Abdominal pain in combination with 3-fold elevation of amylase and/or lipase	Cipro and metronidazole[a]	Cipro 400 mg bid, metronidazole 500 mg bid	14–21 d
			Placebo[b]	NA	14–21 d
Dellinger, 2007[98] USA	Inclusions: Age ≥ 18 y; 30% necrosis of the pancreas by CE-CT; those unsuitable for CE-CT (judgment of investigator) who had non-contrast CT with extensive or multiple fluid collections and pancreatic edema (Balthazar grade E) plus CRP >120 mg/dL or MOD score >2; enrollment within 120 h of onset symptoms Exclusions: Concurrent pancreatic or peripancreatic infection; received an investigational drug within 30 d of study enrollment; antibiotic therapy for > 48 h before enrollment; allergy to β-lactam antibiotics; those who received or were likely to require probenecid or who had progressing underlying disease, neutropenia, or cirrhosis (Child-Pugh class C); pregnancy or lactating females	At least 2 of 3 (pain plus imaging–necrotizing pancreatitis or Balthazar grade E severity pancreatitis)	IV meropenem[a]	1 g IV q8h	7–21 d
			Placebo[b]	Placebo IV q8h	7–21 d
Rokke, 2007[99] Norway	Inclusions: symptoms <72 h, SAP defined by CRP >120 mg/L within first 24 h or >200 mg/L within 48 h or pancreas necrosis on CT scan Exclusions: age <18 y, ongoing antibiotic treatment, post-ERCP pancreatitis, concomitant bacterial infection, such as cholangitis or cholecystitis, allergy to imipenem or pregnancy	AP clinical exam, amylase > 3 times ULN, or CT positivity Not clear how many are needed. Severe selected for study based on CRP at 24 or 48 h exceeding preset limit	IV imipenem[a]	500 mg tid IV	5–7 d
			No antibiotic[b]	—	Until dismissal
García-Barrasa, 2009[100] Italy	Inclusions: Patient without antibiotic treatment and CE-CT evidence of pancreatic necrosis within 48–72 h of admission Exclusions: Quinolone allergy or clinical evidence of sepsis on admission	Conventional (Atlanta) definition: 2 of 3 (typical pain, >3× ULN enzymes and imaging)	IV ciprofloxacin[a]	300 mg IV q12h	10 d
			Placebo[b]	Placebo IV q12h	10 d

Table 4. Continued

First author, year, country	Patient population	AP definition	Nature	Dosage	Duration
Xue, 2009[101] China	Inclusions: AP, CT evidence of >30% necrosis Exclusions: sepsis due to another condition, transfer patient, post-op or post-ERCP pancreatitis, drug allergy to imipenem, other antibiotic use. Post-randomization exclusion for informed consent withdrawal (n = 1 in antibiotic arm, n = 2 in no antibiotic arm)	Not stated, but needed CT confirmation of AP and necrosis	Imepenem[a] Usual care[b]	500 mg tid —	7–14 d 7–14 d

CE-CT, contrast enhanced computed tomography; GN, gram-negative; HU, Houndsfield unit; ICU, intensive care unit; IV, intravenous; MOD, multiple organ dysfunction; NS, normal saline; ULN, upper limit of normal; WBC, white blood cell.
[a]Intervention arm.
[b]Control arm.

included in the review, namely intra-arterial administration of both antibiotics and protease inhibitors[9,10] and selective decontamination of the gut.[11]

Recommendations for future clinical trials on this topic. Future studies should adopt a rigorously adequately powered multicenter trial design to uncover any possible benefits not shown previously due to small sample size. Future studies should also clarify whether specific subgroups may benefit from prophylactic antibiotics, including those with predicted SAP or both extensive sterile necrosis and persistent organ failure, and whether treatment with gut decontamination improves outcomes in patients with predicted SAP (and possibly other subgroups).

Question 3: What Is the Role of Urgent Endoscopic Retrograde Cholangiopancreatography in Acute Biliary Pancreatitis?

Effect of urgent ERCP on the outcomes of mortality, PMOF, PSOF, MOF of unclear duration, single organ failure of unclear duration, infected (peri) pancreatic necrosis, total infected pancreatic necrosis and hospital LOS.

Quality of evidence: Low.

Background information. Gallstones and alcohol are the most common causes of AP. The presumed mechanism by which gallstones cause AP is the temporary obstruction of the ampulla of Vater by a stone, resulting in increased intra-pancreatic duct pressure and subsequent activation of pancreatic digestive enzymes. After triggering AP, most gallstones pass through the ampulla into the duodenum. Therapeutic ERCP emerged in the 1970s as an urgent/emergent biliary drainage procedure in patients with gallstone AP complicated by persistent choledocholithiasis and biliary obstruction, particularly those with acute cholangitis. Treatment typically includes biliary sphincterotomy followed by extraction of biliary stones.

Several RCTs and meta-analyses partially defined the role of urgent ERCP in biliary AP, identifying advantages in some clinical outcomes and contexts but uncertain benefits in others.[48,49] According to 2 recent guidelines, urgent ERCP in biliary AP is indicated when the disease (mild or severe) is complicated by cholangitis,[8,9] is reasonable for persistent biliary obstruction without cholangitis,[9] and is not indicated in the absence of cholangitis or persistent biliary obstruction. Finally, in the absence of cholangitis, the role and timing (<24 hours, <48 hours, or <72 hours) of "therapeutic" ERCP remain unclear in predicted severe biliary AP with persistent biliary obstruction.

As urgent ERCP is indicated and the treatment of choice for acute cholangitis,[50–52] patients with definite AP are generally (especially in more recent trials) excluded from RCTs of urgent ERCP in the setting of acute biliary pancreatitis, yet differentiating cholangitis from persistent biliary obstruction may not always be clinically straightforward. The diagnosis of acute cholangitis is reasonably certain in the presence of Charcot's triad (right upper quadrant abdominal pain, jaundice, and fever) plus leukocytosis, but

Table 5. Antibiotic Prophylaxis: Grading the Evidence

Quality assessment							Patients, n (%)		Effect, OR (95% CI)			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Prophylactic antibiotics	Placebo or standard of care	Relative	Absolute	Quality	Importance
Mortality, n = 10	Randomized trials	Serious[a]	Not serious	Not serious	Serious	None	41/352 (11.6)	60/349 (17.2)	0.66 (0.42−1.04)	51 fewer per 1000 (from 6 more to 92 fewer)[b]	⊕⊕○○ Low	Critical
Infected (peri) pancreatic necrosis, n = 8	Randomized trials	Serious[a]	Not serious	Not serious	Serious	None	51/269 (19.0)	77/260 (29.6)	0.56 (0.36−0.86)	105 fewer per 1000 (from 30 fewer to 165 fewer)	⊕⊕○○ Low	Critical
PMOF or PMODS, NR	—	—	—	—	—	—	—	—	—	—	—	—
PSOF, n = 1	Randomized trials	Serious[a]	Not serious	Not serious	Very serious	None	0/30 (0.0)	1/30 (3.3)	0.19 (0.01−4.06)	27 fewer per 1000 (from 33 fewer to 89 more)	⊕○○○ Very low	Important
MOF or MODS (unclear duration), n = 6	Randomized trials	Serious[a]	Not serious	Not serious	Serious	None	26/226 (11.5)	34/224 (15.2)	0.65 (0.37−1.17)	48 fewer per 1000 (from 21 more to 90 fewer)	⊕⊕○○ Low	Important
SOF (unclear duration), n = 2	Randomized trials	Serious[a]	Not serious	Not serious	Very serious	None	51/80 (63.7)	50/75 (66.7)	0.89 (0.46−1.73)	26 fewer per 1000 (from 109 more to 188 fewer)	⊕○○○ Very low	Important
LOS, n = 3	Randomized trials	Serious[a]	Not serious	Not serious	Very serious	None	66	75	—	MD 4.88 SD lower (10.32 lower to 0.56 higher)	⊕○○○ Very low	Important

MD, mean difference; MOD, multiple organ dysfunction; NR, not reported; PMOD, persistent multiple organ dysfunction; SOF, single organ failure.
[a]Blinding of participants and personnel and blinding of outcome assessment was high.
[b]Subgroup analyses: Among publications after 2002, mortality (n = 384; OR, 0.96; 95% CI, 0.52−1.80) and peripancreatic necrosis (n = 270; OR, 0.81; 95% CI, 0.44−1.49). Similarly, no differences in these 2 outcomes among higher-quality trials (data available upon request).

more definite in the presence of Reynold's pentad (Charcot's triad plus mental confusion and septic shock).[53] Acute cholangitis is less likely when fever and leukocytosis are absent, but remains a possibility when patients have a cholestatic pattern of liver injury, choledocholithiasis, and a dilated bile duct. This clinical ambiguity is an important issue and limitation in many clinical trials of ERCP for biliary AP.

Results of the current systematic review. From 242 citations, we identified 8 RCTs (n = 935) that addressed the role of urgent ERCP in acute gallstone pancreatitis (Supplementary Figure 4a, 4b, and Table 6). Mortality, MOF, single organ failure (respiratory, renal, circulatory), infected (peri) pancreatic necrosis, and total necrotizing pancreatitis were no different between patients randomized to the urgent ERCP or the conservative management groups; subgroup analyses that assessed all studies and those having excluded patients with biliary obstruction showed similar findings. In addition, no differences were attributed to EPCP among patients with pancreatitis and cholangitis, although the outcome was reported in small numbers of patients and in only 1 trial.[54] The only significant difference in outcomes pertained to LOS that was significantly decreased with urgent ERCP WMD = −8.8 (95% CI, −12.64 to −4.96) (1 trial, n = 120 patients).

Although most of the recent trials specifically attempted to exclude patients with suspected cholangitis, there remains marked clinical heterogeneity in adopted selection criteria/definitions limiting the interpretation of the findings (Table 7).

Recommendations for future clinical trials on the topic. Future trials should adopt strict inclusion and exclusion criteria, and definitions for persistent biliary obstruction, cholangitis, and predicted severe biliary AP. These studies should be adequately powered to permit meaningful analysis of all 3 of the latter patient subgroups. The timing of the ERCP intervention should be 24−48 hours after diagnosis (24 hours to allow spontaneous passage of stone and 48 hours to ensure that prolonged biliary obstruction does not occur).

Questions 4, 5, 6: Nutritional Interventions in Acute Pancreatitis

Nutrition and feeding of patients with AP is a broad, complex, and evolving topic. RCTs have compared nil per os (npo) to oral feeding, enteral nutrition to total parenteral nutrition (TPN), types of oral feeding (liquid vs soft vs solid; and escalating vs full diet from the beginning), the timing of oral and enteral tube feeding (early vs delayed), enteral feeding to TPN, and nasogastric (NG) to NJ feeding. Among these comparisons, 3 critical questions (PICO questions 4, 5, and 6) are germane to the management of most patients with AP. It must be recognized, in light of the adopted timelines of interest in medical management for this technical review, that the timing of decisions to initiate feeding may occur within the first 24−48 hours, but may also extend beyond the first 24−48 hours in more severe cases. PICO questions 4, 5, and 6 are inter-related. To avoid redundancy we consolidated the background information for each as 1 section and present it under PICO question 4.

Question 4: What Is the Benefit of Early Feeding in Mild or Severe Pancreatitis?

Effect of early oral feeding on mortality, PMOF, and PSOF, MOF of unclear duration, single organ failure of unclear duration, and infected (peri) pancreatic necrosis, as well as total infected pancreatic necrosis and hospital LOS.

Quality of evidence: Moderate

Background information. Historically, the focus of nutrition and feeding during AP aimed to "rest the pancreas," mainly by providing npo, and removing the food-induced stimulation of exocrine pancreatic secretion, which presumably reduces enzyme-driven inflammation and promotes earlier recovery, and/or to address intolerance to feeding by mouth, namely by fasting or by administering TPN. More recently, the focus has shifted toward protecting the gut−mucosal barrier by initiating enteral feeding, either orally or by enteral tube.

Overall, this approach to patients with AP has mirrored decisions to "resting the gut" during management of other acute abdominal conditions. From a practical standpoint, feeding by mouth is sometimes not feasible in patients with AP (or acute abdominal conditions) who have significant nausea and vomiting (often associated with a paralytic ileus).

TPN was initially recommended to prolong "resting of the pancreas" while avoiding adverse effects of malnutrition associated with fasting. Despite this theoretical advantage, it became apparent that most patients with mild or interstitial AP recover in a very short time and do not require TPN. As a result, administering TPN was restricted to patients with predicted severe or proven necrotizing AP. Clinical use of TPN declined further with accumulation of evidence that enteral feeding had a beneficial trophic effect on the gut−mucosal barrier, thereby reducing bacterial translocation from the lumen into the bloodstream and reducing the risks of infection of (peri) pancreatic necrosis (infected necrosis) and severe outcomes in necrotizing AP. Thus the concept of "gut rousing not gut resting" was introduced.[55]

Recent guidelines have recommended early oral feeding in mild (interstitial) AP.[8,9] In patients with predicted severe or necrotizing AP, hospital stay is typically prolonged and patients are often intolerant to oral feeding. In these latter groups of patients, establishing a definite diagnosis of severe or necrotizing AP usually occurs between 3 and 5 days after initial presentation, a time when NG or NJ feeding was recommended to maintain the gut−mucosal barrier and to prevent infected necrosis. Randomized clinical trials and meta-analyses[56] have demonstrated the superiority of enteral nutrition over TPN with regard to reducing complications (mainly infectious), cost and mortality in predicted severe, and necrotizing types of AP, and rarely in mild AP. A more recent systematic review suggested early oral or enteral tube feeding (within 48 hours) was not associated with any adverse effects in mild to moderate or

Table 6. Urgent Endoscopic Retrograde Cholangiopancreatography in Acute Biliary Pancreatitis: Included Trials

First author, year, country	Patient population	AP definition	Intervention/control
Fan, 1993[102] China	Inclusions: all cases of AP Exclusions: prior attacks showing no stones, post-ERCP pancreatitis, Billroth II, and AC pancreatitis after cardiac arrest	Severe upper abdominal pain with or without radiating to the back and vomiting and amylase >1000 IU/L (nl up to 255 IU/L)	Early ERCP in all cases of AP within 24 h and papillotomy for stones If stone not cleared nasobiliary drainage[a] Conservative management in biliary AP and ERCP only if their condition deteriorated[b]
Fölsch, 1997[103] Germany	Inclusions: age >18 y, AP per definition, only biliary origin (presence of stones or 2/3 liver tests alkaline phosphatase, alanine aminotransferase, and bilirubin meeting criteria) Ability to do ERCP <72 h after pain, written, and informed consent, no pregnancy, coagulation abnormalities or alcohol or metabolic cause, not already in another study, not already included in this study	Upper abdominal pain, amylase, or lipase higher than 3× ULN, US, or CT evidence of AP	Early ERCP within 72 h of onset of pain in biliary AP[a] Conservative management in biliary AP, ERCP performed within and after 3 wk according to preset indications[b]
Neoptolemos, 1988[54] UK	Inclusions: patients suspected to have biliary AP Exclusions: age <18 y, pregnancy, presence of acute or chronic alcohol intake, patients with identifiable cause like drugs, hyperlipidemia, trauma, or surgery	Compatible clinical picture and amylase >1000 IU/L (nl up to 300 IU/L)	Early ERCP in biliary AP and sphincterotomy as needed[a] Conservative management in biliary AP[b]
Zhou, 2002[104] China	Inclusions: acute epigastric pain, history of gallstone, increase in blood and urine amylase, cholelithiasis, cholecystolithiasis, choledocholithiasis, or choledochoectasia detected by US or CT Exclusions: AP due to nonbiliary causes—alcohol, hypercalcemia, hyperlipidemia, trauma	Non-standard diagnostic criteria: epigastric pain, increase in blood and urine amylase (no cutoff values)	Early ERCP in biliary AP, within 24 h of admission (ES was performed for choledocholithiasis with ampullary stenosis to extract stones by basket. Nasobiliary drainage was performed if no stones found or if multiple large stones found that were difficult to extract[a] Conservative management in biliary AP (fasting, hydration, antibiotics, octreotide, antispasmodics, and traditional Chinese medicines)[b]
Acosta, 2006[105] USA	Inclusions: age > 18 y, symptoms consistent with gallstone pancreatitis + ampullary obstruction; admission within 48 h from the onset of symptoms, serum amylase or lipase levels of at least 2× the ULN; serum bilirubin level ≥ 1.4 mg/dL; objective demonstration of gallstones; provision of written informed consent Exclusions: pregnancy; alcoholism or other cause of pancreatitis; severe cholangitis (manifestations of sepsis and requires immediate biliary drainage); coagulation disorder; cirrhosis; contraindication to general anesthesia; Billroth II procedure	Atypical criteria: symptoms consistent with AP but cutoff for serum amylase or lipase was only 2× ULN	Conservative management in biliary AP (with ampullary obstruction): Initial conservative management (broad-spectrum antibiotics, analgesics, NG tube, RUQ US) and systematic ERCP ± ES after 48 h if ampullary obstruction persisted 24 h or longer[a] ±ES after 48 h if ampullary obstruction persisted 24 h or longer[b]

Table 6. Continued

First author, year, country	Patient population	AP definition	Intervention/control
Oria, 2007[106] Argentina	Inclusions: acute upper abdominal pain; serum amylase ≥3× ULN; evidence of pancreatic inflammation on admission CT scan; biliary lithiasis on admission US; absence of other causes of pancreatitis; distal CBD diameter ≥ 8 mm on admission US; serum total bilirubin ≥ 1.2 mg/dL Exclusions: serious comorbid conditions that precluded ERCP; age <18 y; pregnancy; acute cholangitis (defined as RUQ pain, hyperbilirubinemia, axillary temp ≥ 38.4°C); inability to perform endoscopy within 72 h after onset of attack	Acute upper abdominal pain, serum amylase ≥3× ULN and evidence of pancreatic inflammation on admission CT scan Diagnosis of biliary AP also required findings of biliary lithiasis on admission US and absence of other causes of pancreatitis	Early ERCP with ES for bile duct stones in biliary AP within 72 h after admission[a] Conservative management in biliary AP within 72 h after admission. IV Cipro/flagyl administered prophylactically to all and discontinued 7 d after admission, in the absence of pancreatic necrosis[b]
Chen, 2010[107] China	Inclusions: age >18 y, admission within 72 h of symptoms, evidence of AP plus ampullary obstruction for >12 h (severe and continuous pain, bile-free NG aspirate, and elevated bilirubin >50 Umol/L = 2.92 mg/dL), gallstones on US, APACHE II >11 Exclusions: pregnancy, non-biliary pancreatitis, coagulation disorder, cirrhosis, previous Billroth II procedure	Diagnostic criteria not stated, SAP defined by admission to ICU and APACHE II >11	Early ERCP in biliary AP[a] Conservative management in biliary AP[b]
Yang, 2012[108] China	Inclusions: AP 3/3, hospital admission within 72 h of symptom onset; gallstones seen on US, and CBD >8 mm, serum total bilirubin >36 umol/L, and APACHE II >8 or Balthazar CT grading D or E, body temperature ≥38.5°C Exclusions: unfit for ERCP due to serious complications or dyspnea, pregnancy, coagulopathy, cirrhosis, Billroth II surgery, ERCP performed at outside hospital	Definition of acute biliary pancreatitis: acute upper abdominal pain, serum and urine amylase >3× ULN, pancreatitis confirmed by CT scan. Diagnosis of biliary AP also required findings of cholelithiasis or biliary tract dilatation confirmed by type-B ultrasonic and MRCP and absence of other causes of pancreatitis	Early ERCP in biliary AP within 72 h, plus conservative measures noted in control arm[a] Conservative management in biliary AP: fasting, enzyme inhibition, "anti-infection," fluid therapy, nutritional support, ventilator, and ICU when required[b]

AC, acute; CBD, common bile duct; CT, computed tomography; ES, endoscopic sphincterotomy; ICU, intensive care unit; MRCP, magnetic resonance cholangiopancreatography; nl, normal limit; RUQ, right upper quadrant; ULN, upper limit of normal; US, ultrasound.
[a]Intervention arm.
[b]Control arm.

Table 7. Urgent Endoscopic Retrograde Cholangiopancreatography in Acute Biliary Pancreatitis: Grading of the Evidence

Quality assessment							Patients, n (%)		Effect, OR (95% CI)			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Urgent ERCP	Conservative management	Relative	Absolute	Quality	Importance
Mortality, n = 8	Randomized trials	Not serious	Not serious	Serious[a]	Serious[b]	None	24/464 (5.2)	30/471 (6.4)	0.67 (0.26−1.75)	20 fewer per 1000 (from 43 more to 46 fewer)[c]	⊕⊕◯◯ Low	Critical
PMOF or PMODS, NR	—	—	—	—	—	—	—	—	—	—	—	—
MOF (unclear duration), n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	1/60 (1.7)	3/60 (5.0)	0.32 (0.03−3.19)	33 fewer per 1000 (from 48 fewer to 94 more)	⊕⊕◯◯ Low	Critical
SOF (unclear duration)−respiratory failure, n = 5	Randomized trials	Not serious	Serious[d]	Not serious	Serious	None	30/353 (8.5)	30/348 (8.6)	0.86 (0.34−2.19)	11 fewer per 1000 (from 55 fewer to 85 more)	⊕⊕◯◯ Low	Important
SOF (unclear duration)−renal failure, n = 5	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	15/353 (4.2)	14/348 (4.0)	1.02 (0.40−2.59)	1 more per 1000 (from 24 fewer to 58 more)	⊕⊕⊕◯ Moderate	Important
SOF (unclear duration) − circulatory failure, n = 4	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	13/333 (3.9)	14/323 (4.3)	0.99 (0.25−3.95)	0 fewer per 1000 (from 32 fewer to 108 more)	⊕⊕⊕◯ Moderate	Important
Infected (peri) pancreatic necrosis, n = 4	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	5/294 (1.7)	8/286 (2.8)	0.75 (0.21−2.64)	7 fewer per 1000 (from 22 fewer to 43 more)	⊕⊕⊕◯ Moderate	Important
Total necrotizing pancreatitis, n = 4	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	34/283 (12.0)	29/270 (10.7)	1.13 (0.66−1.95)	12 more per 1000 (from 34 fewer to 83 more)	⊕⊕⊕◯ Moderate	Important
LOS, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	60	60	—	MD 8.8 lower (12.64 lower to 4.96 lower)	⊕⊕◯◯ Low	Important

MD, mean difference; NR, not reported; PMOD, persistent multiple organ dysfunction; SOF, single organ failure.
[a]Two studies with unclear biliary pancreatitis, indirectness of population.
[b]Optimal information size not reached.
[c]Subgroup analyses: excluding patients with biliary obstruction: mortality (n = 695) OR, 0.67 (95% CI, 0.18−2.42).
[d]Noted heterogeneity.

predicted SAP, and may even reduce LOS in mild to moderate AP.[57] Few studies have compared NG feeding to NJ (nasoduodenal in some) feeding in predicted severe or necrotizing AP[58] because NG tubes can be placed at the bedside, making it simple and cheap. No differences between the 2 routes of feeding have been noted, although many methodologic problems with these studies preclude a definitive conclusion.[59] To investigate the physiologic benefits attributable to distal duodenal compared to NG feeding, a large multicenter study compared NG to NJ feeding in AP, unfortunately, the trial (ClinicalTrials.gov NCT00580749) was terminated early due to difficulties recruiting patients.

Results from the current systematic review

From 547 citations, we identified 15 RCTs that addressed the role of early vs delayed feeding (Table 8). Four of the 15 were not included in the analyses because timing of feeding was not clearly identified. Mortality was not significantly different for delayed compared to early feeding (OR, 0.59; 95% CI, 0.22−1.59) or any of the other noted outcomes. There exists some clinical heterogeneity in the time to feeding that extends beyond the scope of the first 48 hours targeted by this technical review, varying in part according to the severity of the AP as discussed, but this was not believed to significantly invalidate the results. Subgroup analyses showed no differences in outcomes when comparing npo vs early oral feeding or enteral feeding (data available upon request). However, in the comparison of npo vs early enteral feeding, the rate of intervention for necrosis was increased (OR, 2.47; 95% CI, 1.41−4.35) in the npo (fasting) group (1 trial); in the comparison of npo vs TPN, ICU LOS was significantly shorter for the npo (fasting) group WMD = −10.5 days (95% CI, −15.74 to −5.24 days) (1 trial) (Table 9).

Recommendations for future clinical trials on the topic. In predicted severe and proven necrotizing AP, there is a need to more precisely define the timing of early vs delayed feeding (by oral, NG, or NJ routes) and to investigate whether timing of feeding impacts major outcomes. The value of nutritional additives in enteral nutrition should also be assessed, for example, immuno-nutrition[55] (eg, glutamine) and fiber-enriched formulations.

Question 5: What Is the Benefit of Artificial Enteral Nutritional Support (Nasogastric or Nasojejunal) Compared to Total Parenteral Nutrition in Mild or Severe Pancreatitis?

Effect of artificial nutritional support on the primary outcomes of death, PMOF, and PSOF, MOF of unclear duration, single organ failure of unclear duration, and infected (peri) pancreatic necrosis, as well as total infected pancreatic necrosis and hospital LOS.

Quality of evidence: Moderate

Background information. See the background information to the inter-related PICO question 4 comparing early vs delayed feeding.

Results from the current systematic review. From 547 citations, we identified 12 RCTs that compared NG or NJ to TPN in mild or severe pancreatitis (Table 10). Mortality was not significantly different in the 2 groups (OR, 0.60; 95% CI, 0.25−1.43), but multiple organ failure and single organ failure were significantly decreased in the NG or NJ group compared to TPN (OR, 0.41; 95% CI, 0.27−0.63) and 0.25 (95% CI, 0.10−0.62), respectively. The conclusions were unchanged when restricting the analysis to the trials with only SAP (data available upon request). However, even in severe and necrotizing AP, a proportion of patients can be fed orally, particularly if no significant nausea and vomiting or paralytic ileus is present (Table 11). The evidence supports the superiority of enteral nutrition in both mild and SAP if patients cannot tolerate oral feeding. TPN is indicated only when enteral route is not possible or is not able to meet the minimum calorie requirements.

Recommendations for future clinical trials on the topic. More studies comparing outcomes of enteral feeding to TPN are no longer needed.

PICO 6: What Is the Benefit of the Route of Nasogastric Feeding Over Nasojejunal Feeding in Predicted Severe and Necrotizing Pancreatitis?

Effect of the route of enteral feeding on the primary outcomes of death, PMOF, PSOF, MOF of unclear duration, single organ failure of unclear duration, and infected (peri) pancreatic necrosis, as well as total infected pancreatic necrosis and hospital LOS.

Quality of evidence: Low

Background information. See background information to the inter-related PICO question 4, addressing early vs delayed feeding mentioned previously.

Results from the current systematic review. From 547 citations, we identified 3 RCTs that compared NJ compared to NG in SAP (Table 12). Mortality was not significantly different between the 2 groups (OR, 1.01; 95% CI, 0.44−2.30). Similarly, none of the other outcomes were significantly different for NJ compared to NG. Some methodologic problems exist in these studies, for example, NJ feeding was actually nasoduodenal in 1 study and mortality was higher than usual in the SAP group.[60] Significant weaknesses of these analyses are that each study used different criteria to define SAP, and data for all major outcomes except death were derived from only 1 small study each (Table 13).

Recommendations for future clinical trials on the topic. In predicted severe or proven necrotizing AP, there is a need to more precisely define the optimal route of feeding patients (oral vs NG vs NJ routes) and to determine whether the rate, total calories, and composition of feeds impacts clinically important outcomes.

Question 7: What Is the Role of Same-Admission vs Delayed Cholecystectomy in Patients With Mild Acute Gallstone Pancreatitis?

Effect of same admission vs delayed cholecystectomy on mortality or readmission for gallstone-related complications or mortality during follow-up period (within 6 months of randomization), as well as readmission for

Table 8. Delayed vs Early Feeding: Included Trials

First author, year, country	Patient population	AP definition	Nature	Timing
npo vs oral				
Bakker, 2014[109] Netherlands	Inclusions: all patients with AP who met any of the following: CRP >150 mg/L, APACHE II 8 or more, modified Glasgow score or Imrie score of 3 or more Exclusions: Recurrent acute or chronic pancreatitis, AP due to ERCP or malignancy, pregnancy, receiving enteral or TPN at home, patients more than 24 h from ED admission or >96 h to ED from onset of symptoms	Conventional (Atlanta) definition: 2 of 3 (typical pain, >3× ULN enzymes and imaging)	72 h npo and IVF (exceptions in who asked for oral diet)[a] EN nasoenteral (NJ)[b]	Oral after 72 h Within 24 h of randomization (randomization within 24 h of presentation to ED)
Eckerwall, 2007[110] Sweden	Inclusions: clinical signs of mild AP, pancreatic amylase ≥3 times ULN, onset of abdominal pain within 48 h, APACHE II <8, CRP <150 mg/L Exclusions: Ac pancreatitis due to trauma, surgery, or cancer, short bowel syndrome, IBD, exacerbation of chronic pancreatitis, stoma, pregnancy or age <18 y	Mild AP	npo[a] Immediate oral feeding[b]	Early Early
Zhao, 2015[111] China	Inclusions: moderate or severe pancreatitis based on Atlanta 2012, age >18 y, onset <72 h before admission Exclusions: pregnancy, needing admission to ICU, intubated, requiring surgical intervention	Moderate or severe pancreatitis	npo[a] Early oral[b]	npo until pain resolved and amylase/lipase normal Early oral feeding when hungry, vs based on resolution of abdominal pain and normal lipase/amylase
Ma, 2016[112] New Zealand	Inclusions: diagnosed with AP, ≥18 y of age, gave informed consent Exclusions: severe or critical AP defined by determinant-based classification of AP), chronic pancreatitis, symptoms >96 h, diagnosis of AP during an operation, post-ERCP AP, malignancy, pregnancy, received nutrition before randomization, previously enrolled in trial	Not specified	npo[a] EN (NG)[b]	Early: within 24 h of hospital admission
McKenzie, 2015[113] New Zealand	Inclusions: confirmed diagnosis of AP, ≥18 y of age, and provided written informed consent. Exclusions: >96 h after onset of symptoms; ≥24 h after hospital admission; severe or critical AP; chronic pancreatitis; post-ERCP pancreatitis; intraoperative diagnosis of AP; pregnant; malignancy; received nutrition before randomization; previously enrolled into the trial	Conventional (Atlanta) definition: 2 of 3 (typical pain, >3× ULN enzymes and imaging) defined in referenced publication	npo[a] EN (NG)[b]	Early (within 24 h of admission)

Table 8. Continued

First author, year, country	Patient population	AP definition	Nature	Timing
Powell, 2000[114] UK	Inclusions: AP (defined as history consistent with AP and serum amylase ≥3× ULN) and predicted SAP (defined as Glasgow score ≥ 3 and/or APACHE II score ≥7) Exclusions: age <18 y or >80 y, pregnancy, patients already receiving nutritional support, enrollment in another clinical trial	History c/w AP and serum Amylase ≥3× ULN Predicted SAP defined as Glasgow score ≥3 and/or APACHE II score ≥7	npo[a] EN (NJ)[b]	Within 72 h of onset of symptoms
Li, 2013[115] China	Inclusion: (1) Onset acute abdominal pain with at least 3-fold increase above ULN of amylase and/or lipase; (2) Ultrasound or CT evidence of AP Exclusion: (1) disease onset ≥ 72 h duration before hospital admission; (2) pancreatic neoplasm or post-ERCP pancreatitis; (3) age 18 y or younger, pregnancy or breastfeeding; (4) SAP defined by Ranson's score ≥3 or severe type according to Balthazar CT criteria; (5) patients likely to have poor oral intake or prolonged hospitalization for reasons other than AP (eg, a pre-existing problem with oral feeding, such as gastroparesis, or a surgical intervention during or before the hospital admission)	Same as inclusion criteria	npo until pain resolved and amylase/lipase normal[a] Early oral refeeding[b]	Routine: once subjects fulfilled 4 criteria: (1) no abdominal discomfort; (2) decrease of serum amylase and lipase to <2-fold ULM; (3) normal bowel sounds; (4) subjective feeling of hunger Early: once subjects subjectively developed the feeling of hunger
Teich, 2010[116] Germany	Inclusions: AP, "mild' but not defined Exclusions: none	Need 3/3: symptoms, lipase, and US	npo[a] Oral Oral[b]	Start po when lipase normalized Patient-directed feeding
npo vs TPN				
Sax, 1987[117] USA	Inclusions: AP 2/3	Symptoms, elevated amylase, abnormal KUP (sentinel loop or calcifications)	npo TPN	npo for 7 d, TPN if still unable to eat Within 24 h of admission
Xian-Li, 2004[118] China		Chinese guidelines from 1997, 2/3	npo, including antibiotics, albumin, and "pancreatic enzyme secretion"[a] Standard TPN, antibiotics, "suppression of pancreatic secretion"[b]	
Other				

Table 8. Continued

First author, year, country	Patient population	AP definition	Nature	Timing
Jacobson, 2007[119] USA	Inclusions: AP definition and absence of pancreatic necrosis on contrast CT, absence of organ failure on any day during admission, WBC count <16,000 and temperature <101.6°F and able to be contacted by telephone after hospital discharge Exclusions: Pregnancy, age <18 y, EN before randomization, severe comorbidities, prior problem with oral feeding, gastroparesis or likely surgery during hospitalization, pancreatic neoplasm, under direct care of one of team, previously enrolled in this study or another pancreatitis study	Clinical picture consistent with AP (characteristic abdominal pain lasting ≥ 24 h), amylase and/or >3 times ULN or >2 times ULN with CT showing unequivocal AP with peripancreatic inflammation (Balthazar C, D or E)	Low-fat solid diet Clear liquid diet	npo until team started 1 of the 2 diets npo until 1 of the 2 diets started
Moraes, 2010[120] Brazil	Inclusions (1) upper abdominal pain lasting ≥ 24 h associated with elevated serum amylase and/or lipase >3× ULN and/or CT scan showing unequivocal evidence of AP and (2) mild AP defined by absence or <30% of pancreatic necrosis (if CE-CT scan was performed) and absence of OF (shock, respiratory or renal insufficiency, or GI bleeding) during hospitalization, as defined by Atlanta Exclusions: (1) CE-CT scan with >30% pancreatic necrosis, (2) evidence of OF any time after hospital admission, (3) AP complications requiring surgical intervention, (4) received any nutritional support before randomization, (5) severe comorbidities likely to prolong hospitalization, (6) received parenteral analgesic for abdominal pain within 12 h before randomization, (7) a pancreatic neoplasm as etiology of their pancreatitis, (8) pregnancy or breastfeeding	Conventional (Atlanta) definition: 2 of 3 (typical pain, >3× ULN enzymes and imaging)	Oral hypocaloric clear liquid diet (1 of 3 oral diets) Oral hypocaloric soft diet (1 of 3 oral diets) Oral full solid diet (1 of 3 oral diets)	During first 5 d when medical team felt 3 criteria met: (1) no abdominal pain, nausea and vomiting, or significant abdominal discomfort elicited by palpation; (2) normal bowel sounds; and (3) patient was hungry

Table 8. Continued

First author, year, country	Patient population	AP definition	Nature	Timing
Lariño-Noia, 2014[121] Spain	Inclusions: diagnosis of AP Exclusions: Inability understand study and give informed consent, inability to have oral intake due to causes other than AP, pregnancy, lactation, factors affecting normal pancreatic exocrine function, randomized patients if they are >30 d from onset of symptoms or needing surgery	Acute upper abdominal pain and amylase or lipase >3 times ULN	Oral (bowel sounds present, no abdominal pain, fever, and WBC <15,000 and lipase decreasing) Oral (early when bowel sounds present) Oral (bowel sounds present, no abdominal pain or fever, WBC <15,000 and lipase decreasing) Oral after 24 h fasting (when bowel sounds present, early)	After 24 h fasting After 24 h fasting After 24 h fasting Oral after 24 h fasting
Pandey, 2004[122] India	Inclusions: Consecutive patients admitted with AP who required stoppage of oral feeding for 48 h Exclusions: (1) delay between onset symptoms and refeeding of >30 d; (2) already on oral feeds at presentation; (3) acute exacerbation of chronic pancreatitis; (4) need for surgery to treat complications of AP	3/3 criteria: Acute abdominal pain with elevated serum amylase or lipase >5× ULN and US or CT evidence of AP	Oral feeding EN (NJ)	Standard when treating physician considered the patient to be pain free and ileus subsided

CT, computed tomography; ED, emergency department; EN, enteral nutrition; GI, gastrointestinal; ICU, intensive care unit; IVF, intravenous fluid; KUP, radiographic study of the kidneys, ureter, and bladder. OF, organ failure; ULN, upper limit of normal; US, ultrasound; WBC, white blood cell.
[a]Intervention arm.
[b]Control arm.

Table 9. Delayed vs Early Feeding: Grade of the Evidence

Quality assessment							Patients, n (%)		Effect, OR (95% CI)			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delayed	Early feeding	Relative	Absolute	Quality	Importance
Mortality, n = 6	Randomized trials	Not serious[a]	Not serious	Not serious	Serious[b]	None	7/371 (1.9)	11/358 (3.1)	0.59 (0.22−1.59)	12 fewer per 1000 (from 17 more to 24 fewer)	⊕⊕⊕○ Moderate	Critical
PMOF or PMODS, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	4/104 (3.8)	4/101 (4.0)	0.97 (0.24−3.99)	1 fewer per 1000 (from 30 fewer to 102 more)	⊕⊕○○ Low	Critical
PSOF, n = 2	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	25/175 (14.3)	32/168 (19.0)	0.69 (0.38−1.24)	51 fewer per 1000 (from 35 more to 108 fewer)	⊕⊕○○ Low	Critical
PSOF− respiratory failure, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	14/104 (13.5)	12/101 (11.9)	1.15 (0.51−2.63)	15 more per 1000 (from 54 fewer to 143 more)	⊕⊕○○ Low	Critical
Infected (peri) pancreatic necrosis, n = 3	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	20/205 (9.8)	12/197 (6.1)	1.69 (0.80−3.60)	38 more per 1000 (from 12 fewer to 128 more)	⊕⊕○○ Low	Important
MOF (unclear duration), n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	6/104 (5.8)	3/101 (3.0)	2.00 (0.49−8.22)	28 more per 1000 (from 15 fewer to 171 more)	⊕⊕○○ Low	Important
Total necrotizing pancreatitis, n = 2	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	26/101 (25.7)	16/96 (16.7)	1.84 (0.88−3.86)	102 more per 1000 (from 17 fewer to 269 more)	⊕⊕○○ Low	Important

PMOD, persistent multiple organ dysfunction.
[a]Blinding of participants and personnel and Blinding of outcome assessment was high, it was not judged to have an impact on the outcomes for this PICO.
[b]Optimal information size not reached, all trials except one were double zero event.

Table 10. Artificial Enteral Nutritional Support (Nasogastric or Nasojejunal): Included Trials

First author, year, country	Patient population	AP definition and target condition	Nature	Timing of feeding
Abou-Assi, 2002[123] USA	Inclusions: All patients with AP who did not improve after 48 h of npo and IVF Exclusion: None	Acute abdominal pain and 3-fold elevation of amylase and lipase Mild and severe pancreatitis	EN NJ after[a] TPN with bowel rest[b]	48 h of IVF and npo After 48 h of npo and IVF
Doley, 2009[124] India	Inclusions: clinical features, hyperamylasemia 3× ULN, CT pancreas necrosis, and CTSI ≥7 Exclusions: chronic pancreatitis, intervention before admission, inotropic support requirement, or complications requiring interventions at admission	AP not separately stated except SAP definition Severe pancreatitis	NJ beyond LOT[a] TPN[b]	
Eckerwall, 2006[125] Sweden	Inclusions: abdominal pain, amylase +/>3 times ULN, onset of abdominal pain within 48 h, APACHE II +/> 8, CRP +/> 150 mg/L, peripancreatic liquid on CT Exclusions: AP due to surgery, trauma, or cancer, IBD, stoma, short bowel, chronic pancreatitis with exacerbation	Not specified Predicted severe	NG[a] TPN[b]	Within 24 h from admission Within 24 h from admission
Gupta, 2003[126] UK	Inclusions: APACHE II ≥ 6 Exclusions: pregnancy, age ≤16 y	Abdominal pain and serum amylase ≥ 1000 U/L (nl up to 300 U/L) Severe pancreatitis predicted	NJ[a] TPN[b]	Immediate within 24 h of randomization Within 48 h
Kalfarentzos, 1997[127] Greece	Inclusions: Imrie ≥3, APACHE II >8, CRP > 120 mg/L in 48 h, Balthazar Grade C or D Exclusions: patients treated elsewhere for > 2 d before admission to the hospital	Not specified Severe (all necrotizing)	NJ[a] TPN[b]	Within 48 h Within 48 h
Louie, 2005[128] Canada	Inclusions: Required to have AP + Ranson's score ≥ 3 (measured at 48 h) + inability to tolerate fluids after maximum time from admission of 96 h Exclusions: <18 y of age, unable to accept EN via GI tract, already receiving nutritional support	Not specified Predicted SAP	NJ[a] TPN[b]	96 h (same as comparator: inability to tolerate fluids after maximum 96 h) 96 h (same as comparator: inability to tolerate fluids after maximum 96 h)
McClave, 1997[129] US	Inclusions: AP or acute flare of chronic pancreatitis, characterized by abdominal pain and elevation of serum amylase or lipase Exclusions: short bowel syndrome, Crohn's disease, major pancreatic resection, or failure to start EN or TPN within 48 h of admission After study entry, patients were excluded if they failed to adhere to dietary restrictions or the protocol terms for enteral tube placement	Not specified Mostly mild severity AP (not otherwise specified as part of inclusion/exclusion criteria)	EN (NJ)[a] TPN[b]	Within 48 h of admission (same as comparator arm) Within 48 h of admission (same as comparator arm)

Table 10. Continued

First author, year, country	Patient population	AP definition and target condition	Nature	Timing of feeding
Olah, 2002[130] Hungary	Inclusions: (1) Clinical sx, (2) plasma amylase ≥2.86× ULN, and (3) admitted within 24 to 72 h after onset of symptoms Exclusions: (1) biliary tract disease (because patients required other therapeutic interventions); (2) acute flares of chronic pancreatitis; (3) placement of feeding tube not possible (unable to cooperate or repeatedly removed feeding tubes); (4) intolerant to jejunal feedings	Unconventional: Clinical sx plus plasma amylase ≥ 2.86× ULN All severity AP	EN (NJ)[a] EN + prophylactic imipenem for pancreatic necrosis[a] TPN[b]	Within 24 h EN within 24 h; imipenem median 3.8 d Within 24 h
Petrov, 2006[131] New Zealand	Inclusions: Predicted SAP. AP defined as upper abdominal pain plus serum amylase ≥3× ULN. SAP defined as: an APACHE II score of 8 or more and/or CRP >150 mg/L Exclusions: age <18 years or pregnancy	Upper abdominal pain plus serum amylase ≥3× ULN Predicted SAP, defined as: an APACHE II score of 8 or more and/or CRP > 150 mg/L	EN (NG)[a] TPN[b]	Within 72 h of onset of symptoms (same as comparator) Within 72 h of onset of symptoms (same as comparator)
Wang, 2013[132] China	Inclusions: Age 18−45 y; duration of abdominal symptoms ≤48 h; presence of GI ileus or distension Exclusions: chronic kidney disease; pregnancy or breastfeeding; planned dialysis, plasmapheresis, or other treatment requiring extracorporeal blood removal; IBD; infections at the time of admission to the hospital; recent NSAID use	3/3 criteria SAP	Enteral nutrition, using NJ tube and elemental formula[a] TPN[b]	NS, admitted within 48 h of onset of symptoms NS, admitted within 48 h of onset of symptoms

CT, computed tomography; CTSI, computed tomography severity index; EN, enteral nutrition; GI, gastrointestinal; IBD, inflammatory bowel disease; IVF, intravenous fluid; nl, normal limit; NS, normal saline; NSAID, nonsteroidal anti-inflammatory drug; ULN, upper limit of normal.
[a]Intervention arm.
[b]Control arm.

Table 11. Artificial Enteral Nutritional Support (Nasogastric or Nasojejunal): Included Trials

Quality assessment							Patients, n (%)		Effect, OR (95% CI)			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NJ/NG	TPN	Relative	Absolute	Quality	Importance
Death, n = 12	Randomized trials	Not serious	Serious[a]	Not serious	Not serious	None	32/404 (7.9)	59/422 (14.0)	0.60 (0.25−1.43)	51 fewer per 1000 (from 49 more to 101 fewer)	⊕⊕⊕◯ Moderate	Critical
PMOF or PMODS	—	—	—	—	—	—	—	—	—	—	—	—
PSOF	—	—	—	—	—	—	—	—	—	—	—	—
PSOF−respiratory failure, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	5/18 (27.8)	7/20 (35.0)	0.71 (0.18−2.84)	73 fewer per 1000 (from 255 more to 262 fewer)	⊕⊕◯◯ Low	Important
PSOF−renal failure, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	2/18 (11.1)	3/20 (15.0)	0.71 (0.10−4.81)	39 fewer per 1000 (from 133 fewer to 309 more)	⊕⊕◯◯ Low	Important
Infected (peri) pancreatic necrosis, n = 6	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	39/207 (18.8)	94/216 (43.5)	0.28 (0.15−0.51)	258 fewer per 1000 (from 153 fewer to 332 fewer)	⊕⊕⊕◯ Moderate	Important
MOF (unclear duration), n = 6	Randomized trials	Not serious	Serious[a]	Not serious	Serious[b]	None	45/287 (15.7)	86/292 (29.5)	0.41 (0.27−0.63)	148 fewer per 1000 (from 86 fewer to 193 fewer)	⊕⊕◯◯ Low	Important
SOF, n = 3	Randomized trials	Not serious	Not serious	Not serious	Very serious[b]	None	7/96 (7.3)	25/97 (25.8)	0.25 (0.10−0.62)	178 fewer per 1000 (from 81 fewer to 224 fewer)	⊕⊕◯◯ Low	Important
Total necrotizing pancreatitis, n = 5	Randomized trials	Not serious	Not serious	Not serious	Serious[b]	None	130/208 (62.5)	131/216 (60.6)	1.15 (0.65−2.05)	33 more per 1000 (from 106 fewer to 153 more)	⊕⊕⊕◯ Moderate	Important

PMOD, persistent multiple organ dysfunction; SOF, single organ failure.
[a]Noted heterogeneity.
[b]Optimal information size not reached.

Table 12. Nasogastric Feeding over Nasojejunal Feeding: Included Studies

First author, year, country	Patient population	AP definition	Nature	Timing of feeding
Eatock, 2005[60] UK	Inclusions: Glasgow score ≥3 or more, APACHE II ≥6, and CRP ≥150 mg/L Exclusions: none	Abdominal pain and serum amylase at least 3× ULN Severe pancreatitis	NG[a] NJ[b]	Within 48 h of admission Within 48 h of admission
Kumar, 2006[133] India	Inclusions: presence of OF, APACHE II≥ 8, CTSI ≥ 7 Exclusions: delay of > 4 wk from the onset of symptoms, already taking oral feeding, acute exacerbation of CP, or in shock at presentation (systolic BP <90 mm Hg)	Not specified Severe pancreatitis	NG[a] NJ (actually ND placed into third part of duodenum)	48 h of admission 48 h of admission
Singh, 2012[134] India	Inclusions: SAP admitted within 7 d of onset of symptoms Exclusions: already on feeds, shock, not willing to provide consent	3/3 diagnostic criteria. SAP defined as OF, necrosis, or APACHE II >* SAP	Early NG feeding[a] NJ[b]	Within 48 h of admission Within 48 h of admission

BP, blood pressure; CP, chronic pancreatitis; CTSI, computed tomography severity index; ND, nasoduodenal; OF, organ failure; ULN, upper limit of normal.
[a]Intervention arm.
[b]Control arm.

recurrent pancreatitis, and pancreaticobiliary complications, conversion to open cholecystectomy, difficulty of cholecystectomy, and need for additional interventions

Quality of evidence: Moderate

Background information. Gallstones, along with alcohol, are the most common causes of AP. Numerous cohort studies provide evidence that cholecystectomy reduces the risk of subsequent attacks of gallstone pancreatitis[61–64] and failure to perform timely cholecystectomy results in a substantial risk of biliary complications that escalates over time, including recurrent gallstone pancreatitis or other biliary complications.[62,64–66] According to a recent systematic review, readmission rates averaged 18% at 6 weeks after an index stay for biliary pancreatitis in the subset with gallbladder in situ.[67] In those who are unsuitable surgical candidates, biliary sphincterotomy reduces the risk of developing recurrent gallstone pancreatitis, but not other biliary complications.[67–70] The timing of cholecystectomy for gallstone pancreatitis is controversial (and is the focus of 2 RCTs,[71,72] but outside the focus of this PICO). In mild AP, older medical and surgical guidelines recommend cholecystectomy at variable times ranging from the index hospitalization to several weeks after hospital discharge. Clinical practice has similar variability, which reflects factors that support or oppose early cholecystectomy, both knowledge of risks of recurrent biliary complications without performing cholecystectomy, but also challenges with surgical scheduling and concerns about data quality and the safety and operative risks in the setting of active inflammation and potentially altered anatomy. Recent guidelines[8,9] and a recent systematic review[67] recommend same-admission cholecystectomy for mild, interstitial pancreatitis, and provide additional recommendations for more severe cases. In mild AP attributed to gallstones, cholecystectomy is recommended during the index hospitalization (moderate quality of evidence). In those with moderate to severe acute gallstone pancreatitis having (peri) pancreatic collections, surgery should be postponed until "active inflammation subsides and fluid collections resolve or stabilize"[73] after approximately 6 weeks.[9] Delaying cholecystectomy in moderate to severe disease appears to reduce morbidity,[67] including infected collections[74] and mortality.[71] These latter observations are further supported by recent retrospective observations that inadvertent underestimation of severity of acute gallstone pancreatitis is associated with increased complications in those undergoing cholecystectomy during the index hospitalization.[75]

Results of the current systematic review. From an initial 120 citations, we identified only 1 RCT (n = 264) that addressed the role of same admission vs delayed cholecystectomy in patients with mild acute gallstone pancreatitis (Table 14). Same-admission cholecystectomy

Table 13. Nasogastric Feeding Over Nasojejunal Feeding: Grading the Evidence

Quality assessment							Patients, n (%)		Effect, OR (95% CI)			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NJ	NG	Relative	Absolute	Quality	Importance
Death, n = 3	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	17/82 (20.7)	15/75 (20.0)	OR 1.01 (0.44–2.30)	2 more per 1000 (from 101 fewer to 165 more)	⊕⊕○○ Low	Critical
PMOF or PMODS, NR	—	—	—	—	—	—	—	—	—	—	—	—
PSOF, NR	—	—	—	—	—	—	—	—	—	—	—	—
PSOF–renal failure, NR	—	—	—	—	—	—	—	—	—	—	—	—
PSOF–respiratory failure, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	7/27 (25.9)	8/22 (36.4)	OR 0.61 (0.18–2.08)	105 fewer per 1000 (from 179 more to 270 fewer)	⊕⊕○○ Low	Important
Infected pancreatic necrosis, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	3/16 (18.8)	3/14 (21.4)	OR 0.85 (0.14–5.07)	26 fewer per 1000 (from 178 fewer to 366 more)	⊕⊕○○ Low	Important
MOF, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	15/39 (38.5)	11/39 (28.2)	OR 1.59 (0.62–4.11)	102 more per 1000 (from 86 fewer to 335 more)	⊕⊕○○ Low	Important
SOF, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	10/39 (25.6)	15/39 (38.5)	OR 0.55 (0.21–1.45)	129 fewer per 1000 (from 91 more to 269 fewer)	⊕⊕○○ Low	Important
Necrotizing pancreatitis, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	17/39 (43.6)	19/39 (48.7)	OR 0.81 (0.33–1.98)	52 fewer per 1000 (from 166 more to 249 fewer)	⊕⊕○○ Low	Important
Interventions for necrosis, n = 2	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	3/55 (5.5)	6/53 (11.3)	OR 0.45 (0.11–1.89)	59 fewer per 1000 (from 81 more to 99 fewer)	⊕⊕○○ Low	Important
Need for ICU, n = 1	Randomized trials	Not serious	Not serious	Not serious	Very serious[a]	None	7/27 (25.9)	8/22 (36.4)	OR 0.61 (0.18–2.08)	105 fewer per 1000 (from 179 more to 270 fewer)	⊕⊕○○ Low	Important

NR, not reported; PMOD, persistent multiple organ dysfunction.
[a]Optimal information size not reached.

Table 14. Same-Admission vs Delayed Cholecystectomy: Included Trials

First author, year, country	Patient population	AP definition	Intervention	Control
Da Costa, 2015[135] Netherlands	Inclusion: first episode gallstone AP (12/7/2010−8/14/2013), Age ≥18 y, CRP <100 mg/L, no need for opioid analgesics, tolerance of a normal oral diet at time of randomization Exclusion: ASA class III in those ≥ 75 y, all ASA class IV, chronic pancreatitis, ongoing alcohol use, pregnancy	2 of 3 criteria Mild pancreatitis was defined by absence of persistent organ failure (ie, > 48 h), and local complications, such as pancreatic necrosis or peripancreatic fluid collections on CT	Early cholecystectomy	Interval (delayed) cholecystectomy

ASA, American Society of Anesthesiologists; CT, computed tomography.

was done within 3 days after randomization. In the interval cholecystectomy group, patients were discharged from hospital and cholecystectomy was electively scheduled 25−30 days after randomization. Intraoperative cholangiography was not mandatory, with widespread availability of ERCP, if indicated. The primary end point was a composite of gallstone-related complications or mortality occurring within 6 months after randomization, before or after cholecystectomy, analyzed by intention to treat. Gallstone-related complications were defined as readmission for recurrent pancreatitis, cholecystitis, cholangitis, choledocholithiasis needing ERCP or gallstone colic. The primary end point occurred in significantly fewer patients in the surgery during the same admission group compared to those undergoing delayed cholecystectomy (OR, 0.24; 95% CI, 0.09−0.61); no difference was noted in mortality during the 6-month follow-up period (OR, 3.21; 95% CI, 0.13−79.56). Patients undergoing same-admission cholecystectomy had significantly fewer readmissions for both recurrent pancreatitis and pancreaticobiliary complications compared to those undergoing delayed cholecystectomy (OR, 0.25; 95% CI, 0.07−0.90 and OR, 0.24; 95% CI, 0.09−0.61, respectively). There was no difference between conversion to open cholecystectomy or difficulty of cholecystectomy between the 2 groups (Table 15).

Recommendations for future clinical trials on the topic. Future studies should further clarify the optimal timing of laparoscopic cholecystectomy during the index hospitalization for mild AP in the modern era, and also determine the optimal timing of cholecystectomy for severe necrotizing pancreatitis. Additional issues that require study include whether to routinely screen for local (peri) pancreatic collections using predictive tools or cross-sectional imaging to triage patients to early vs delayed surgery, the role of endoscopic sphincterotomy as a bridge to cholecystectomy in patients with more severe pancreatitis,[76,77] and the elaboration of predictive tools to exclude patients with moderately severe or severe pancreatitis who might require a delay in cholecystectomy.

Question 8: What Is the Role of Alcohol Counseling in the Management of Patients With Acute Pancreatitis?

Effect of alcohol counseling on total hospital admissions, recurrent pancreatitis (second attack), definite recurrent pancreatitis, likely recurrent pancreatitis, and 2 or more recurrent attacks pancreatitis, as well as alcohol abstinence, alcohol consumption in grams per 2 months, Short Alcohol Dependence Data questionnaire (scale, 0−45), and laboratory markers of alcohol use.

Quality of evidence: Moderate

Background information. Alcohol remains one of the more common causes of AP. In most analyses, some degree of chronic pancreatic injury is present at the time of the first clinical attack, suggesting a prolonged period of subclinical injury before presentation with AP. Pancreatitis does not appear to occur from isolated binge drinking,[78] and generally requires several years of ongoing substantial alcohol use. Of importance, <5% of patients with significant alcohol use will develop pancreatitis.[79] These data suggest that additional cofactors are necessary to confer susceptibility to pancreatitis associated with alcohol, including risk factors (eg, smoking, genetic susceptibility, dietary factors, heredity, and alcohol type) and protective factors (eg, caffeinated coffee). Once pancreatitis develops, it can be severe, and chronic pre-existing alcohol use is a risk factor for pancreatic necrosis (regardless of the primary cause) and higher mortality from the initial episode of AP. A recent report suggested that recurrent attacks occurred in 24% after an attack of acute alcoholic pancreatitis and chronic pancreatitis developed in 16% of them.[80] Alcohol and smoking were independently associated with progression to chronic pancreatitis and had additive risk. Surprisingly, smoking, but not alcohol, was associated with risk of recurrences. Abstinence from alcohol (and also tobacco) after the first attack is recommended to reduce the risk of diseases related to these toxins (ie, cirrhosis and lung cancer), reduce the risk of secondary pancreatic malignancy, and reduce the risk of subsequent episodes of pancreatitis. Abstinence also slows or decreases the risk of evolution to advanced chronic

Table 15. Same-Admission vs Delayed Cholecystectomy: Grading the Evidence

Quality assessment							Patients, n (%)		Effect, OR (95% CI)			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Same-admission	Delayed	Relative	Absolute	Quality	Importance
Mortality and composite gallstone-related complications, n = 1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	6/128 (4.7)	23/136 (16.9)	OR 0.24 (0.09−0.61)	123 fewer per 1000 (from 59 fewer to 151 fewer)	⊕⊕⊕◯ Moderate	Critical
Mortality during follow-up period (within 6 mo of randomization), n =1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	1/128 (0.8)	0/136 (0.0)	OR 3.21 (0.13−79.56)	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕⊕◯ Moderate	Critical
Readmission for recurrent pancreatitis, n = 1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	3/128 (2.3)	12/136 (8.8)	OR 0.25 (0.07−0.90)	65 fewer per 1000 (from 8 fewer to 82 fewer)	⊕⊕⊕◯ Moderate	Critical
Readmission for pancreaticobiliary complications, n = 1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	6/128 (4.7)	23/136 (16.9)	OR 0.24 (0.09−0.61)	123 fewer per 1000 (from 59 fewer to 151 fewer)	⊕⊕⊕◯ Moderate	Important
Conversion to open cholecystectomy, n = 1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	5/128 (3.9)	4/136 (2.9)	OR 1.34 (0.35−5.11)	10 more per 1000 (from 19 fewer to 105 more)	⊕⊕⊕◯ Moderate	Important
Difficulty of cholecystectomy, n = 1	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	On a 1−10 visual analogue scale: interval cholecystectomy; 6 (4−7) compared to same-admission cholecystectomy 6 (4−7); $P = .70$				⊕⊕⊕◯ Moderate	Important

[a]Optimal information size not reached.

pancreatitis, particularly pancreatic function,[81] while effects on reducing pain are inconsistent.[82] There are no trials comparing specific efforts at smoking cessation and relapses of AP, although multiple lines of evidence support the benefit of achieving smoking cessation in non-pancreatic diseases, but such intervention is not addressed by a PICO in this technical review.

Results from the current systematic review. From 63 citations, we identified only 1 RCT that addressed the role of alcohol counseling on recurrent bouts of AP (Table 16). The included patients had a clear alcohol history and had undergone a first attack of AP with the exclusion of other possible etiologies. Comparing similar interventions of alcohol counseling as a sole session at the initial hospitalization vs every 6 months for 2 years in a gastrointestinal clinic setting, a strong trend favored the repeated intervention for the outcome of total hospital admission rates (OR, 0.38; 95% CI, 0.14−1.00), with nonsignificant differences noted for the other outcomes of a second attack of pancreatitis (OR, 0.34; 95% CI, 0.11−1.03), definite recurrent pancreatitis (OR, 0.34; 95% CI, 0.11−1.03), or 2 or more recurrent attacks of pancreatitis (OR, 0.56; 95% CI, 0.16−2.03). Additional outcomes were not assessed in the trial (Table 17). An important limitation of this analysis is, of course, the paucity of randomized trials available in the literature in the context of patients with AP.

Additional pertinent data from a systematic review in a different patient population from which the information may be applied to patients with AP. A Cochrane review of alcohol-reduction strategies was also considered; while the trials this systematic review refers to were not carried out in the context of patients presenting with AP, the effect of an intervention strategy was assessed in a large number of studies (22 RCTs) and evaluated outcomes in >5800 patients.[83] Patients who received a brief intervention had a significant reduction in alcohol consumption compared with controls after 1 year (−38 g/wk; 95% CI −54 to −23 g/wk), although substantial heterogeneity between trials was noted and the benefit of brief intervention was statistically significant in men but not in women. Extended intervention was associated with a nonsignificantly increased reduction in alcohol consumption compared with brief intervention. In the absence of any dose threshold linking alcohol intake to AP and its recurrence, and in the absence of any significant untoward effects related to the proposed intervention, this evidence was applied to the PICO under consideration, while the level of evidence was downgraded for indirectness and chosen outcomes.

Recommendations for future clinical trials on the topic. Future studies should focus on patients with a first attack of alcoholic pancreatitis, and should include both separate and combined efforts at alcohol and tobacco cessation. Outcomes of interest could include recurrent attacks, progression to chronic pancreatitis, need for further intervention for necrosis, quality of life, health care utilization and cost, development of subsequent pancreatic cancer, and mortality.

Question 9: What Is the Clinical Impact of Utilizing a Risk Assessment Severity Prediction Tool?

Background information. Authors of past and recent clinical guidelines[8,9] for managing AP recommend that clinicians predict the severity of AP during the early phase of the condition. The goals of using these predictive tools are to help identify sicker patients, allowing patient triage to the appropriate level of care (eg, intensive care unit) or to treatments appropriate for sicker individuals (enteral feeding), but also to identify those with milder disease, who might be candidates for earlier hospital discharge. Although in the absence of any specific therapy that can be applied to those predicted to have a severe or moderately severe course, the clinical utility of predictive tools can be questioned. A multitude of predictive tools are available for use, including clinical scoring systems (eg, APACHE II, Glasgow-Imrie score, and Japanese severity score), patient characteristics (eg, body mass index, age), single or multiple laboratory markers (BUN, creatinine, CRP), some of which have been used dynamically to assess the patient's response to care over time (eg, SIRS and BUN). A recent report actually suggested that current scoring systems have reached their limit to predict persistent organ failure with

Table 16. Alcohol Counseling: Included Studies

First author, year, country	Patient population	AP definition	Descriptor	Nature of counseling	Frequency	Duration
Nordback, 2009[136] Finland	Inclusions: AP due to clear alcohol history and first attack and other etiologies excluded Exclusions: Other etiologies of AP or not the first attack of alcoholic AP	2 of the 3 accepted criteria with no prior attack	Repeated interventions[a]	30-min intervention (three 10-min portions)	Every 6 mo for 2 y in the GI clinic	2 y
			Single intervention[b]	Same 30-min intervention only once at admission in hospital	Once at admission	Only at initial admission

GI, gastrointestinal.
[a]Intervention arm.
[b]Control arm.

Table 17. Alcohol Counseling: Grading of the Evidence

	Question: Should HCV screening followed by BAI vs no intervention be used for hazardous or dependent drinking?[83]										
							Study event rates, %			Anticipated absolute effects	
Participants (studies), follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	With no intervention	With HCV screening followed by BAI	Relative effect (95% CI)	Risk with no intervention	Risk difference with HCV screening followed by BAI (95% CI)
Quantity of drinking, *g/wk* (critical outcome; Better indicated by lower values) n = 5860 (22 RCTs)	No serious risk of bias	No serious inconsistency	No serious indirectness[a]	Serious imprecision[b]	Undetected	⊕⊕⊕◯ moderate	2922	2938	—	Mean quantity of drinking in the control groups was 313 g/wk alcohol[c]	Mean quantity of drinking in the intervention groups was 38.42 g/wk lower (65.44−30.91 g/wk lower)

BAI, brief alcohol intervention; HCV, hepatitis C virus.
[a]Although the BAI was not specifically targeted to patients with AP, the panel thought that a new diagnosis of acute alcoholic pancreatitis in combination with a BAI if likely even more effective than BAI alone. Not downgraded for indirectness.
[b]Only 1 trial looked at population with AP.
[c]21 trials reported baseline alcohol consumption: range 89 to 456 g/wk; overall mean 313 g/wk (26 standard US drinks [∼12 g each]/wk; 3.7 average/d).

no good positive predictive value and future research should include novel approaches.[84] In another recent systematic review, no single tool is favored and most tools have only moderate predictive value for predicting development of persistent organ failure or infected pancreatic necrosis.[85] For this reason, there is general consensus from guidelines and among experts to utilize expert clinical judgment and a variety of predictive tools to best estimate predicted severity. An initial 1260 citations were retrieved from the systematic literature search and 839 full-text articles were reviewed. What is lacking in the literature are specific studies focused on whether utilizing a risk severity assessment tool during the early management of AP impacts outcomes, which would match the aim of the systematic review of identifying interventions or treatments that impact outcomes, and more specifically the a priori−set objective for this PICO. A single study that comes closest to addressing this question focused on whether use of tools to predict severity (SIRS, BISAP [Bedside Index for Severity in Acute Pancreatitis], or transient organ failure) coupled with a structured management approach would impact outcomes.[86] Whereas the structured management of AP compared to usual care in historical controls has been shown to be associated with a significant reduction in hospital LOS without affecting other major outcomes (eg, persistent organ failure or pancreatic necrosis), it is difficult to tease apart the individual contribution of such predictors on any clinically important outcome. Moreover, all predictors have tried to prognosticate SAP and the only study that attempted to predict the moderately severe type of AP found it impossible to distinguish this entity from SAP.[87]

Results of the current systematic review. All of the reasons mentioned, and the absence of any observational study or RCT on the clinical impact of using severity prediction tools, prevented us from identifying any gradable evidence.

Recommendations for future clinical trials on the topic. There is a need to identify predictive markers or tools that are accurate in prognosticating both moderately severe and SAP during the initial 24−72 hours. In addition, measuring clinical outcomes in groups with and without the use of such tools is also required, but clinically pertinent only if a drug or other specific therapy is available to treat AP.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.01.031.

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Conflicts of interest
The authors disclose no conflicts.