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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