



New guidelines for the treatment of severe acute pancreatitis

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Severe forms of pancreatitis account for 15–20% of acute pancreatitis cases, with a mortality rate approaching 20% (1,2). Patients with this condition manifest components of multisystem organ failure, rapid decompensation, and life-threatening complications arising both early and late in the disease course. The clinical decline can be difficult to predict, and treatments are typically supportive and reactive, rather than preventative (3). These factors pose complex challenges during treatment, which has evolved over the past decade and requires a team approach to management.

The French Society of Anesthesia and Intensive Care Medicine (SFAR) Clinical Guidelines Committee convened in June, 2021, to formulate updated recommendations, “*Guidelines for the management of patients with severe acute pancreatitis, 2021*”, published in *Anaesth Crit Care Pain Med* (4) with both written and graphical Editorials (5,6). The multidisciplinary expert committee was composed of specialists from intensive care medicine, gastroenterology, endoscopy, radiology, and clinical nutrition. The guidelines answer 14 critical questions informed by studies from the year 2000 onward and include 20 distinct recommendations formulated with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system. All recommendations were then validated by expert vote and found to have strong (>70%) agreement using the GRADE Grid method. Additionally, there were four questions which were deemed unanswerable by the current state of literature (absence of recommendation) and another four on which expert opinion was proposed. The recommendations based on these 14 questions are found in *Table 1*.

When comparing these guidelines to those formulated

by the International Association of Pancreatology (IAP) and American Pancreatic Association (APA) in 2013 (7) and the American Gastroenterological Association (AGA) in 2018 (8), most of the recommendations are consistent. Early oral or enteral nutrition is recommended over parenteral nutrition with the aim of reducing infectious complications and mortality. Nasojejunal tubes are not recommended over nasogastric tubes to improve the tolerance of enteral feeding, and both elemental or traditional polymeric mixtures are appropriate. Antibiotic prophylaxis for sterile necrosis is unlikely to reduce mortality or the rate of local or systemic infection. Drainage of infected necrosis using a graduated step-up approach starting with percutaneous or endoscopic drainage is preferred over initial surgery. Urgent endoscopic retrograde pancreatography as an intervention during acute biliary pancreatitis is not recommended unless there is evidence of concomitant cholangitis.

The only disagreement between guidelines is regarding initial fluid management. IAP/APA recommends goal-directed therapy with 5–10 mL/kg/h until noninvasive or invasive targets are reached, and that early resuscitation within 24 hours decreases rates of persistent systemic inflammatory response syndrome and organ failure. The AGA agrees with goal-directed therapy, but does not specify rate of fluid nor type, although hydroxyethyl starch is not to be used. Opposing this view are the SFAR guidelines, which state aggressive vascular loading during the first 24 hours as an initial fluid resuscitation strategy is not recommended. Rather, it should be based on initial hemodynamic response to fluid administration, without specifying further.

A very recent randomized controlled trial that supports the SFAR guidelines with more conservative fluid

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Table 1 Summary of recommendations

SFAR recommendation	IAP/APA	AGA
Field 1: Evaluation and admission to critical care of the adult patient		
(2+) Intensive care unit admission probably recommended for patients with organ failure with or without necrosis, or acute pancreatitis at risk of becoming severe	Agree	–
(1+) CT scan recommended if diagnosis unclear after history and lipase levels, if clinically worsening, or if not responding to initial treatment	Agree	–
(1+) Liver enzymes, triglycerides, calcium, and abdominal ultrasound routinely recommended	Agree	–
(1+) Intraabdominal pressure monitoring recommended in the first 72 h if invasively ventilated	Agree	–
Field 2: Treatment during the initial phase		
(2–) Resuscitation with 3–5 mL/kg/h during the first 24 h probably not recommended to reduce mortality, acute kidney injury, or hospital length of stay; rather, base it on results of hemodynamic response	Disagree	Disagree
(2–) Probiotics probably not recommended to reduce mortality or respiratory complications	Agree	–
(1+) Enteral nutrition recommended over parenteral nutrition to reduce mortality, systemic infection, and possibly local infection	Agree	Agree
(1–) Systematic implementation of early enteral nutrition (24–48 h) not recommended over later nutrition to reduce mortality, infections, or organ failure	–	–
(1–) Systematic nasojejunum tubes not recommended over nasogastric tubes to improve feeding tolerance	Agree	Agree
(2–) Semi-elemental or elemental mixtures and immuno-nutrition probably not recommended over standard polymeric mixtures for enteral feeding	Agree	–
(2+) If parenteral nutrition required, supplementation with intravenous glutamine probably recommended to reduce mortality, infections, and length of stay	–	–
(2–) Additive antioxidants to nutritional formula probably not recommended	–	–
(1+) In biliary pancreatitis, urgent ERCP only recommended for cases of cholangitis	Agree	Agree
(2–) Unconventional drug therapies (somatostatin, insulin, nonsteroidal anti-inflammatories, various other small molecules) probably not recommended	–	–
(EO) Therapeutic plasma exchange recommended for hypertriglyceridemia >1,000 mg/dL if not rapidly reduced with fibrates, insulin, and heparin	–	–
Field 3: Treatment and management of progressive complications		
(2–) Prophylactic antimicrobials probably not recommended to reduce mortality, infected necrosis, or other infections	Agree	Agree
(2+) Procalcitonin and CT scan probably recommended over C-reactive protein for diagnosing infected necrosis	–	–
(EO) Fine needle aspiration for diagnosing infected necrosis not recommended in the absence of clinical signs of sepsis or gas on CT scan	Agree	–
(2+) Drainage of infected necrosis probably recommended over just antibiotics alone	Agree	–
(1+) A graduated, step-up approach with endoscopic or percutaneous needle drainage recommended	Agree	–
(EO) Transfer to an adequately equipped center recommended if no minimally invasive drainage options	Agree	–
(2+) Antibiotic coverage targeting resistant <i>Enterobacter</i> species, <i>Enterococcus faecium</i> , <i>Pseudomonas aeruginosa</i> , and yeast probably recommended	–	–
(EO) Direct fluid sampling or positive blood cultures to guide targeted antibiotic selection	–	–
(2+) Endovascular treatment for gastrointestinal hemorrhage probably recommended over open surgical approach	–	–

Recommendation strength: 1+: recommended; 2+: probably recommended; 1–: not recommended; 2–: probably not recommended; EO: expert opinion. SFAR, French Society of Anesthesia and Intensive Care Medicine; IAP, International Association of Pancreatology; APA, American Pancreatic Association; AGA, American Gastroenterological Association; CT, computed tomography; ERCP, endoscopic retrograde cholangiopancreatography.

administration enrolled 249 patients at 18 centers with a new diagnosis of pancreatitis of unspecified severity. Patients were randomized to aggressive fluid resuscitation with 20 mL/kg followed by 3 mL/kg/h or moderate fluid resuscitation with 10 mL/kg or no bolus followed by 1.5 mL/kg/h, and assessed at regular intervals in the first 72 hours. The trial was halted in its first interim analysis for safety concerns, as 20.5% of patients developed fluid overload in the aggressive fluid resuscitation arm and only 6.3% in the moderate resuscitation arm [adjusted relative risk (ARR), 2.85; 95% confidence interval (CI): 1.36–5.94; $P=0.004$]. There was no difference in the incidence of the primary outcome, which was the development of moderately severe or severe pancreatitis (22.1% vs. 17.3%; ARR, 1.30; 95% CI: 0.78–2.18; $P=0.32$) (9).

Several new additions by the SFAR are included that are not in the IAP/APA or AGA guidelines. There has not been consistent benefit demonstrated for enteral nutrition when comparing semi-elemental, elemental, and immunonutrition options to standard polymeric mixtures. Additive antioxidants or other unconventional drug therapies like somatostatin, insulin, or nonsteroidal anti-inflammatories have also not yet shown benefit. There does appear to be evidence that intravenous glutamine offers a benefit when added to parenteral nutrition formulae in reducing mortality, infections, and length of stay, but not when added to enteral nutrition. Procalcitonin levels may add some additional benefit over C-reactive protein for diagnosing uncertain cases of infected necrosis. While a specific choice for antibiotic is not recommended, broadly covering resistant *Enterobacter* species, *Enterococcus faecium*, *Pseudomonas aeruginosa*, and yeast is recommended. Lastly, endovascular treatment is recommended over open surgical approach to gastrointestinal hemorrhage.

Questions unable to be addressed in the current guidelines due to insufficient evidence included ventilation strategy, method of analgesia, particular antibiotic choice, and necessity of anticoagulation for confirmed splanchnic venous thrombosis or for those at high risk for thrombosis. The group also weighed in to advocate for therapeutic plasma exchange in cases of severe hypertriglyceridemia, mitigating use of fine needle aspiration for diagnosing infected necrosis unless imperative due to possibility of complications and high rate of false negatives (20–25%) (10), encouraging transfer to a center with skilled interventional gastroenterology and radiology services in cases necessitating drainage of infected pancreatic necrosis, and narrowing antibiotics based on positive blood cultures or results acquired from fluid drained

directly from the infected necrosis.

While the guidelines were authored by a diverse group of clinicians, including 14 intensivists, two gastroenterologists, two endoscopists, two radiologists, and one clinical nutritionist, it is notable that no surgeons were included. Surgical expertise is particularly valuable for this patient population even though the management paradigm for peripancreatic fluid collections and pancreatic necrosis has shifted away from early surgical intervention. After medical stabilization, time is an ally. The maturation (arbitrarily, of 4 weeks or greater) of sterile fluid collections to pancreatic pseudocysts and pancreatic necrosis to walled-off necrotic collections, allows safer and less invasive approaches like endoscopic and percutaneous drainage. Patients can manifest ischemic injury to intraabdominal organs requiring early surgical intervention, and, although interventional radiologic approaches to hemorrhagic complications are preferred, on occasion surgery is recommended. Conditions like abdominal compartment syndrome, infected necrosis, disconnected duct syndrome, pseudocyst, and enteric fistula are best managed with a multidisciplinary team involving surgeons in order to bring all possible approaches and tailor treatment for each patient.

The publication of the “*Guidelines for the management of patients with severe acute pancreatitis, 2021*”, captures the evidence-based changes that have evolved over the last two decades, and the accompanying graphic is pragmatic and useful during bedside clinical decision making. We applaud the efforts of this multidisciplinary expert group to improve the clinical care for these complex patients suffering from a highly morbid disease.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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