Review article

Clinical update on fluid therapy and nutritional support in acute pancreatitis

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Background/objectives: The aim of this focused review is to provide a valuable and updated source of information for clinical practice on fluid therapy (FT) and nutritional support in acute pancreatitis (AP).

Methods: The review encompasses important new clinical information that has become available for understanding and offering these specific treatments since the 2013 publication of two guidelines, both the joint International Association of Pancreatology and American Pancreatic Association and the American College of Gastroenterology. The 2015 Revised Japanese Guideline is discussed selectively. To this end, the review is divided into 7 sections, including timing and cause of mortality; severity classification systems; predicting severity; response to treatment; nutritional support; fluid therapy and steps for further research.

Conclusions: In mild AP, begin oral feeding when nausea, vomiting and abdominal pain are improving. In (predicted) severe AP, feeding decisions should commence by 72 h, offering oral feeding if GI symptoms improve or enteral feeding if patients are symptomatic and/or intolerant to orals. All patients should be offered goal-directed FT during the first 6–12 h of presentation. Cautious FT is advised in those age >55 years or with preexisting organ failure or predictors of developing fluid sequestration.

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Timing and cause of mortality

Mortality in acute pancreatitis (AP) ranges 1–9% overall [1,2] and increases to up to 20–25% in those with severe acute pancreatitis (SAP) [3]. Key determinants of death are multi-organ failure (MOF) [3–5] and infected (peri)pancreatic necrosis (IPN) [6,7]. During the initial 2-weeks of AP death is attributable predominantly to ≥1 persistent organ failures (POFs), particularly multi-organ failure (MOF) [3–5]. The term organ failure (OF) applies to renal, respiratory and circulatory organ systems, and requires having a Marshall score of at least 2 [8]. The Revised Atlanta Classification defines transient organ failure (TOF) as ≤48 h and persistent organ failure (POF) as >48 h [5]. Overall, approximately 40% of deaths occur within the first 7 days [3]. Mortality escalates from 0 to 2.5% in those with no OF up to 27–36% with POF and 47% with MOF [3]. MOF develops in approximately 10–15% of patients with AP [9] and begins most commonly with respiratory followed by renal failure [10]. In a study of 1024 cases of fatal AP, all had evidence of OF, 63% had at least 2 OFs [10], and the median time to death was 3 days after onset of OF and 6 days after onset of AP [10]. During weeks 2–6 of AP, death is predominantly due to complications of infected (peri)pancreatic necrosis (IPN) [5–7]. In a meta-analysis of 14 AP studies with 1478 patients, individual and combined IPN and POF influenced mortality [6]. Mortality was 11% in IPN without POF, 22% in POF without IPN and 43% with both IPN and POF.

Severity classification systems

Two severity classification systems [5,7] evolved and replace the original 1992 Atlanta Classification [11]. The Revised Atlanta Criteria (RAC) [5] and the Determinants Based Classification (DBC) [7] differ by the development process, the grades of severity (3 vs. 4) and whether IPN is included (only for DBC). Despite these differences, both severity classifications are comparable and complementary for predicting need for ICU admission, ICU length of stay (LOS), hospital LOS, need for intervention and mortality [12–16].
Predicting severity

Recent AP guidelines published by the American College of Gastroenterology (ACG) [17] and the joint International Association of Pancreatology (IAP) and American Pancreatic Association (APA) [18] recommend different approaches for predicting SAP.

ACG guidelines caution that AP-specific predictive scoring systems have limited value and clinicians should broadly consider patient characteristics (age >55 years [19,20]; BMI >30 (kg/m²) [21,22]; altered mental status, comorbid disease), presence of ≥2 systemic inflammatory response syndrome (SIRS) criteria [4,23,24], factors associated with hypovolemia (BUN >20 mg/dl [25], rising BUN [25], elevated Hct [26,27], and elevated creatinine [28]) and radiologic findings (pleural effusions and/or pulmonary infiltrates [29] and extra-pancreatic collections). The guideline omits additional clinical risk stratification tools that have comparable predictive values (e.g. Japanese Severity Score, BISAP score, etc) [30,31].

IAP/APA guidelines recommend a structured “3-dimensional assessment” focused on host risk factors, prognostic tools and monitoring response to therapy.

Host risk factors: There is abundant data that increasing age (≥50–80 years) associates with increasing systemic complications in AP [19,20,32–37]. For example, two predictive scoring systems include age ≥55 years as associated with increased AP severity [19,20]. Three representative studies illustrate that increasing age associates with increasing mortality [32–34]; mortality was 28% for age ≥60 years [33] and 30–40% for age >80 [32,34]. Body mass index (BMI [kg/m²]) ≥30 associates with increased severity and mortality in AP on the basis of a recent systematic review [38] and a meta-analysis [22]. Comorbid illnesses are important “host risk factors” but do not appear to independently predict more severe outcomes [35–37].

Prognostic tools are numerous but generally comparable for predicting SAP [31,39,40]. Use of SIRS score ≥2 is advantageous [17,18] due to simplicity and the increasing predictive value of repeated measurements [4,23,24]. On admission, SIRS ≥2 ≥2 associates with 7% mortality (100% sensitive and 31% specific) [4,10,23,24] and SIRS <2 associates with almost 100% negative predictive value (NPV) for SAP [24] and up to 100% NPV for mortality [4], but (SIRS <2) cannot necessarily guarantee survival. Persistent SIRS ≥2 for ≥48 h associates with 25% mortality (77–89% sensitive, 79–86% specific) [4,10,23,24].

Recommended methods to monitor response to therapy are serial measurements of SIRS (see above) [4,23,24], serum BUN [25] and creatinine [28]. An elevated or rising BUN associates with increased mortality [25].

Response to treatment

A key management question is whether enteral nutrition (EN) or IV fluid therapy (FT) can reverse or prevent complications and death in AP. According to the IAP/APA Working Group (2013) [18], EN reduces OF and mortality [41,42] compared to parenteral nutrition (PN) and FT reduces SIRS, OF, infections and death but not pancreatic necrosis [18].

Nutritional support

AP guideline recommendations [17,18]: In mild AP begin oral feeding when nausea, vomiting and abdominal pain improve. A low fat diet appears as safe as clear liquids [43]. In SAP, oral feeding may begin with onset of hunger (typically after a mean 8 days [44]), which may shorten hospital LOS [44]. EN is recommended due to a lower risk of infectious complications compared to PN [41,42,45]. Timing of EN is discussed separately. Nasogastric tube feeding does not reduce patient quality of life compared to nil by mouth [46] and feeding by nasogastric or nasojejunal routes have comparable effectiveness and safety [47–49], as do polymeric and the more expensive (semi)elemental formulations [50,51].

Nutritional adjuncts are not recommended by recent AP guidelines [17,18,30] including: probiotics, immunonutrition (e.g. with glutamine) and fiber enriched formulations. There is insufficient supportive evidence that probiotics are beneficial [52,53] and significant yet unexplained [54] safety concerns [52]. There is also no evidence [50,55] that immunonutrition (e.g. with glutamine) is helpful and fiber enrichment is not discussed in any of the guidelines [17,18,30]. Similarly, conclusions of the 2015 Cochrane Database Systematic Review [51] are that further research is required to determine if immunomodulatory agents improve clinically meaningful outcomes (a possibility supported by a meta-analysis of 10 heterogeneous studies [56]) and that “Evidence remains insufficient to support the use of a specific EN formulation”. PN should be avoided unless the alternative is no feeding, the latter which carries a higher risk of mortality but not infection compared to PN [51,57].

Critical care: Early EN is standard treatment for critically ill patients [58,59]. In a meta-analysis beginning early EN (within vs. after 36 h of admission or surgery) associated with fewer infectious complications (19% vs. 41%, P = 0.0006) [60] and in a prospective cohort of 1176 critically ill patients beginning early EN (within vs. after 48 h) associated with lower mortality in the ICU (23% vs. 28%, P = 0.03) and hospital (34% vs. 44%, P < 0.001) [61].

In AP, the Cochrane Database Systematic Review [41] and guidelines [17,18,62–64] stated that EN was superior to PN. EN is 10-fold less costly and reduces the risk of infections through unclear mechanisms, possibly by maintaining gut barrier function and glycemic control [65]. In data pooled from meta-analyses [42,66,67] EN compared to PN for patients with predicted SAP had a lower risk for developing infectious complications (OR = 0.24–0.48) [42,66,67], ≥2 OFs (OR = 0.33) [66,67], and mortality (OR = 0.25–0.32) [42,66,67]. Moreover, in systematic reviews initiating EN within 24–48 h had the greatest benefit [67,68]. For example, Bakker et al. [68] analyzed a “single arm” of 8 RCTs that included data for patients receiving EN within 24 h (n = 100) and after 24 h (n = 65). Early EN associated with a reduction in the 3-variable composite endpoint (19% vs. 45%, P < 0.05), which included infected necrosis (7% vs. 14%, P = NS), OF (16% vs. 42%, P < 0.05) and death (3% vs. 12%, P = NS).

Contrary to expectations, Dutch investigators, who performed a 19-center RCT of 208 patients with predicted SAP, found that early EN (begun within 24 h of randomization) was not superior to on-demand oral feeding (begun 72 h after presentation) or EN if oral diet was not tolerated [69]. Both study arms had a similar frequency of the individual variables major infection (25% vs. 26%, P = 0.87) and death within 6 months (11% vs. 7%, P = 0.33) and of the composite endpoint (30% vs. 27%, P = 0.76). Whether this major undertaking is a definitive study is the focus of two editorials [70,71]. Four concerns are that 1) the majority of the patients (2/3) did not have actual treatment; 3) 40% of feeding tubes were dislodged, which further reduced the potential benefit of early EN treatment; and 4) other parallel treatments were not controlled, including FT and opiates use.

IV fluid therapy (FT)

Historically, FT is thought to mitigate the hypovolemic shock that commonly accompanies AP, by improving pancreatic microvascular perfusion, thereby improving outcomes [72–77].

ACG, Revised Japanese and IAP/APA guideline recommendations [17,18,30]. Lactated ringers FT is preferred initially [17,18,30], based on a single RCT [78]. ACG guidelines [17] recommend “aggressive
hydration" for all patients (except for those with renal or cardiovascular insufficiency) at an initial rate of 250–500 mL/h (6–12 L/24 h), “more rapid repetition (bolus)" for “hypotension and tachycardia”, with the goal of reducing serum BUN levels [25]. Revised Japanese Guidelines recommend “short-time rapid" FT with 150–600 mL/h to correct shock and dehydration before transitioning to a maintenance rate of 130–150 mL/h [30]. IAP/APA guidelines [18] recommend goal directed FT at a rate of 5–10 mL/kg/h (6–17 L/24 h), typically ranging 2.5–4.0 L/24 h, until one or more goals are achieved, including noninvasive (HR < 120 bpm; MAP 65–85 mmHg; Hct 35–44%; or urine output >0.5–1 mL/kg/h) or invasive (stroke volume or intra-thoracic blood volume determination) measurements.

In 2001, a landmark RCT of patients with sepsis established a survival benefit of early goal-directed FT during an early 6 h therapeutic window [79] but this concept is not supported by a series of 3 inter-related RCTs published in the New England Journal of Medicine [80] and a systematic review and meta-analysis [81]. Several differences should be noted between the landmark and recent studies. "Usual-care" of sepsis has evolved over 15 years and the negative study by Mouncey et al. [80] enrolled patients who were less sick (e.g. lower mean plasma lactate), received antibiotics prior to randomization, and were randomized at a later time in the Emergency Department (median 2.5 h) [80] vs. median 1 h [79]). Overall, these paradigm shifting observations beg for a critical appraisal about the role of aggressive FT/goal-directed FT in AP and other acute diseases, as outlined earlier by De-Madaria and Garg [82].

The concept of early goal directed FT permeates the AP literature but the data in AP "remains paltry and of poor quality" and inconclusive for recommending rates and type of FT and whether higher rates prevent or contribute to clinical outcomes [83]. Two main limitations of these studies are errors of reverse causation bias [82] and that FT begins after onset of AP when the “therapeutic window” is closing. In SAP, FT is frequently >5 L during the initial 24 h [84] but the clinical benefit may be limited to the initial 12 h [76,85]. More is not always better [17,18]. Two RCTs from China reported a higher frequency of complications (e.g. sepsis, respiratory failure, compartment syndrome and mortality) with more rapid (aggressive) FT, defined as rapid vs. slow hemodilution within 48 h, aiming for a target hematocrit <35% vs. >35%, respectively [86], and rapid vs. controlled fluid expansion, at rates of 10–15 mL/kg/h vs. 5–10 mL/kg/h, respectively [87]. These RCTs substantiate concerns from retrospective studies that adverse outcomes associate with administration of more aggressive early FT [88–91], even when the volume of FT appears modest (>4 L/24 h) [88,89].

To model harm from aggressive FT, de-Madaria [92] retrospectively examined risk factors and outcome of developing fluid sequestration during the first 48 h after hospital admission. Five variables independently predicted fluid sequestration: younger age, alcohol etiology, hematocrit, glucose and SIRS [92]. Median fluid sequestration was 3.2 L and increasing volumes associated with longer hospital LOS and higher rates of acute fluid collection, pancreatic necrosis and POF [92]. Fluid sequestration had no significant association with mortality, but according to others, fluid sequestration associates with intra-abdominal hypertension (IAH) [93] and progression to abdominal compartment syndrome (ACS), which increases mortality and hospital/ICU utilization for patients with AP [94]. Two AP guidelines [18,30] and the World Society of the Abdominal Compartment Syndrome (WACS) differentiate IAH from ACS based on intra-abdominal pressure (IAP), measured via the bladder, and organ dysfunction. IAH is defined by a persistently elevated IAP >12 mmHg and ACS is defined by IAP >20 mmHg plus new organ dysfunction/failure.

Standardized FT protocols are lacking for AP [76,77] but several studies applied goal-directed approaches [40,78,86,96]. The FT suggested at the University of Michigan (Table 1) illustrates a goal-directed algorithm, adapted from our previously published version [40]. We emphasize the initial 12 h of presentation as the time to achieve FT goals (see below) and underscore the importance of cautious FT in the elderly and those with preexisting OF. Goal-directed FT for patients with predicted mild AP or SAP is recommended due to potential under- or late recognition of SAP, arising from severity misclassification or evolution of SAP. We recommend infusing lactated ringers initially [17,18,78] at rates of 5–10 mL/kg/h until patients are hemodynamically stable (HR < 120 bpm, MAP 65–85 mmHg, urine output >50 ml/h) [18,40,76–79,87,97]; beginning maintenance FT rates at 3 mL/kg/h [40,78,85,97]; and adjusting FT every 6 h by whether BUN is <20 mg/dl or falling [17–20,25,40,78,98,99].

Bolus vs. brisk infusion: It is unclear whether there is more than a semantic difference between beginning FT in AP as a vigorous fluid bolus (20–30 mL/kg) or a brisk rate of resuscitation. Fluid boluses have been advocated for treatment of AP [97,100] and sepsis/shock [79,101] but boluses have the potential to “over-shoot" goals because they are ordered as discrete, all-or-none volumes. In part to avoid “over-shotting" the Michigan algorithm recommends an initial brisk rate of FT (as part of a structured goal-directed algorithm), which conceptually allows for quickly switching over to a maintenance rate when goal-directed limits are achieved. Moreover, the recommended initial FT rate of 5–10 mL/kg/h is incorporated in the IAP/APA guideline and is a safety decision derived from evidence within one of the few FT RCTs focused on AP; higher rates of initial FT (10–15 mL/kg/h or >5–10 mL/kg/h) associate with worse outcomes [87], as discussed above.

FT begun at the onset of AP has promise for treating AP based on the results of both experimental [73,75,76,102–104] and post-ERCP pancreatitis (PEP) studies [105–107]. FT given before or during induction of AP improves survival in dogs (50% vs. 9%) [102] and in mice (67% vs. 31%) [103] but does not prevent onset of AP [102,103] and does not maintain pancreatic perfusion after onset of microcirculatory damage, typically within 8 h of AP onset [75]. In two cohort PEP studies greater peri-procedural IV FT associated with a shorter hospital LOS [106] and was an independent predictor of less severe PEP [105]. Moreover, peri-procedural IV FT was not significantly different, between PEP and no PEP groups [105], mirroring the experimental AP observations that prophylactic FT does not prevent onset of AP [102,103]. Interestingly, in one small, pilot RCT PEP was less frequent with aggressive vs. standard IV FT [107].
Nonetheless this result should be interpreted with caution because of the small study size (n = 62 patients) and methods as discussed in the accompanying editorial [108].

The optimal fluid type for FT remains controversial in AP [73,75,76]. Conceptually, crystalloid vs. colloid solutions expand different fluid compartments, plasma plus interstitial space vs. plasma, respectively, and require different volumes to restore the circulation, large vs. less, respectively. In experimental AP, FT with crystalloid associates with reduced survival compared with hypertonic saline [109] or various colloids, including albumin [72], high molecular weight (HMW) dextran [110], plasma [118], and purified bovine hemoglobin [119,120]. Investigators of the few RCTs of FT in AP [78,121,122] report that lactated ringers (LR) vs. normal saline associates with less frequent SIRS [78] and FT with hydroxyethyl starch (HES) vs. LR associates with less intra-abdominal hypertension [121]. Results of more conclusive critical care RCTs, however, indicate no benefit of any colloid (including HES) vs. crystalloid [123–128].

Steps for further research

Future studies are necessary to more precisely define the timing of EN in (predicted) SAP, the appropriate rate and whether nutritional adjuncts (e.g., immunonutrition) improve outcomes. Trials are needed to determine the optimal criteria for hydration in AP, particularly among those at increased risk for fluid sequestration and negative outcomes; whether invasive hemodynamic monitoring (e.g., Pulse indicator Continuous Cardiac Output (PiCCO) system [129]) or less invasive approaches can guide FT in high risk patients in a way that impacts outcomes; to verify the feasibility and outcome of FT administered by nasojejunal rather than intravenous route in patients with severe AP [130]; and to explore the retrospective preliminary finding that combining early EN and aggressive FT shortens hospital LOS, and reduces intensive care unit admissions and severe AP [131].

Summary

I selectively review the 2013 ACG & IAP/APA guidelines and the 2015 Revised Japanese guideline on AP and new data relevant to clinical practice. This includes new definitions for predicting and diagnosing SAP and the approach, timing and impact of two specific therapies: nutritional support and FT. Feeding recommendations in mild AP are to begin oral feeding when nausea, vomiting and abdominal pain are improving. In SAP, feeding decisions should commence by 72 h, offering oral feeding if GI symptoms improve or EN if patients are symptomatic and/or intolerant to orals. Regardless of severity, all patients should be offered goal-directed FT during the first 6–12 h of presentation. Cautious FT is advised in those age >55 years or with preexisting OF or predictors of developing fluid sequestration.

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References


[92] de-Madaria E, Banks PA, Moya-Hoyo N, Wu BU, Rey-Rivero M, Acvedo-Pedra NC, et al. Early factors associated with fluid sequestration and out-


[96] Reddy N, Wilcox CM, Tamhane A, Eloubeidi MA, Varadarajulu S. Protocol-


[98] Wu BU, Johannes RS, Sun X, Tabak Y, Conwell DL, Banks PA. The early pre-


[100] Nacar JY, Papachristou GI. Early fluid resuscitation in acute pancreatitis: a lot more than just fluids. Clin Gastroenterol Hepatol Off Clin Pract J Am Gas-


[104] Knol JA, Inman MG, Strodel WE, Eckhauser FE. Pancreatic response to crys-
talloid resuscitation in experimental pancreatitis. J Surg Res 1987;43:


ciation of greater intravenous infusion with shorter hospitaliza-


[108] Elmunzer BJ. Aggressive intravenous fluid resuscitation for preventing post-

[109] Shields CJ, Winter DC, Sookhai S, Ryon L, Kirwan WO, Redmond HP. Hy-

[110] Anderson MC, Lewis MB. Low-molecular-weight dextran therapy in exper-


[129] Sun Y, Lu ZH, Zhang XS, Geng XP, Cao LJ, Yin L. The effects of fluid resusci-


[131] Szabo FK, Fei L, Cruz LA, Abu-El-Hajia M. Early enteral nutrition and aggressive fluid resuscitation are associated with improved clinical out-