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Severe acute pancreatitis in the community: confusion reigns

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ABSTRACT

Background: The management of acute pancreatitis (AP) has evolved through enhanced understanding of the disease. Despite several evidence-based practice guidelines for AP, our hypothesis is that many hospitals still use historical treatments rather than adhere to the current guidelines, which have demonstrated shorter hospital stays, decreased infectious complications, decreased morbidity, and decreased mortality.

Materials and methods: Seventy-eight patients transferred to our institution with AP from 2010–2014 were retrospectively studied to compare pretransfer *versus* posttransfer adherence to current practice guidelines. Primary measures included use of antibiotics (abx), enteral nutrition, drainage of asymptomatic pseudocysts, and interventions for necrosis in the early phase (<4 wk).

Results: Pretransfer, abx were given to 51 patients; however, posttransfer, abx were discontinued in 33 patients and started in 6 patients within 24 h of admission (pretransfer *versus* posttransfer abx, 51 *versus* 24, $P < 0.001$). Empiric abx for AP were used in 36 patients pretransfer *versus* 9 patients posttransfer ($P < 0.001$). Patients were initially nil per os or on total parenteral nutrition in 89%; this was reduced to 17% within 72 h by starting a diet or enteric feeds (pretransfer *versus* posttransfer feeding, 9 *versus* 65 patients, $P < 0.001$). Fifteen transfer patients had pseudocysts that were believed to "require drainage"; five patients received intervention but >4 wk from initial episode of AP. Pretransfer, five patients had pancreatic debridement in the early phase, which resulted in prolonged postoperative length of stay compared with eight patients requiring debridement, which were delayed (early *versus* late, 56 *versus* 16 d, $P < 0.05$).

Conclusions: There is still great confusion in the treatment of AP in community hospitals. Primary principles in the care of these patients are not routinely followed despite established guidelines. Increased dissemination is required to prevent lengthy hospitalizations and long-term morbidity.

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1. Introduction

In the last decade, there have been several substantial developments in the treatment of acute pancreatitis (AP). Clinically, up to 20% of patients with AP are classified as severe [1]; however, improved understanding of the pathophysiology of organ failure in severe AP and outcomes of necrotizing pancreatitis have made it necessary to revise the previously universally accepted Atlanta Classification system for AP [2]. The new 2012 revision, created by an international consensus, was to provide more objective terms to describe the terminology of severe AP and its complications based on the natural history of the condition and better imaging techniques available [3,4]. Local complications of AP are defined as peripancreatic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), pseudocysts, and walled-off necrosis. Mortality of necrotizing pancreatitis ranges from 15% in patients with sterile necrosis to up to 40% in those with infected necrosis, which can occur at some point in the clinical course in about one-third of patients with necrosis [1,5,6]. The care of patients with severe AP or necrotizing pancreatitis should ideally include a team of specialists in intensive care medicine, gastroenterology, interventional endoscopy, interventional radiology, and surgery. However, there remains a wide variation in clinical practice as physicians with quite varied training (surgical *versus* medical, and so forth) and experience may be responsible for managing these patients.

Recognition of the challenges of managing this complex disease has been the impetus for a number of publications reviewing the different treatments and techniques in the management of AP. Recently, the American College of Gastroenterology published practice guidelines for AP patients based on a systematic literature search, added commentary, and remarks from leading pancreatologists worldwide and a critical appraisal of the evidence according to the Grading of Recommendations, Assessment, Development, and Evaluation approach to systemic reviews and guideline development. This was focused largely on early medical management strategies, but included a discussion of the sequelae of complicated disease (necrotizing pancreatitis) in efforts to advance our understanding of this disease process and decrease overall morbidity and mortality. These practice guidelines specifically cover the evolving issues of hydration, antibiotics (abx), nutrition, timing, and type of minimally invasive interventions (endoscopic and surgical) in severe AP [7]. Similarly, the leadership of both the International Association of Pancreatology and the American Pancreatic Association have published evidence-based guidelines for the multidisciplinary management of AP, again addressing the key clinical questions as follows: diagnosis, prediction of severity, imaging, fluid therapy, intensive care management, preventing infections complications, nutritional support, biliary tract management, indications, timing and intervention strategies for necrotizing pancreatitis, and timing of cholecystectomy [8].

However, despite the public availability of these widely accepted guidelines, as well as the educational programs sponsored by many society meetings—offering a multidisciplinary, evidence-based approach with concrete recommendations on the key aspects of medical and surgical management of AP—our hypothesis is that many hospitals still use outdated, anecdotal treatment practices in managing AP, rather than making the change to strictly adhere to the current best practice guidelines that should serve as a new reference standard for the current management of AP.

2. Materials and methods

2.1. Patients and clinical data collection

All patients transferred to Stanford University Medical Center with the diagnosis of AP from 2010–2014 were identified by searching our prospective database maintained by the Stanford Hospital adult transfer center. Specific patient data were retrospectively collected using our hospital electronic medical record after institutional review board approval was obtained. Patient charts, radiology reports, and procedure notes were reviewed to compare pretransfer (referring hospital) *versus* posttransfer (home institution) transfer adherence to practice guidelines for the management of AP. Primary measures examined included use of empiric abx, absence of enteral nutrition, need for drainage of routine pseudocysts, and intervention for pancreatic necrosis in the early phase (<4 wk). Our standard initial approach to patients with severe AP who were transferred to our institution is listed in the Figure.

2.2. Statistical analysis

Continuous data are expressed as mean ± standard error of the mean for parametric data or median (interquartile range [IQR]) for nonparametric data. Categorical variables are reported as number and percentage. Continuous variables were compared by Student *t*-test (laboratory values) and the Mann–Whitney *U* test when data were not normally distributed. Categorical frequencies were compared by Fisher exact test; statistical significance was set at $P < 0.05$ for all comparisons. Descriptive statistical analysis was performed using GraphPad Prism version 6.00 for Windows; GraphPad Software, La Jolla, CA, www.graphpad.com.

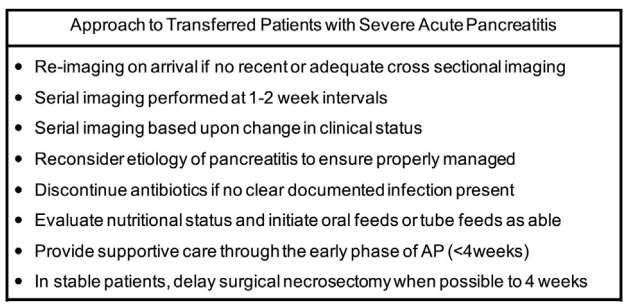

Figure – Optimization of patient care in patients with severe AP.

3. Results

3.1. Demographics of the transferred AP patients

A query was made to the Stanford Hospital adult transfer center for the patients transferred to our institution with a diagnosis of AP. Between April 2010 and April 2014, the query resulted in 100 patients. There were 78 patients with a correct diagnosis of AP (mild and severe cases) that were transferred from 45 different local community hospitals for further clinical management. The average distance of transfer was 93 (range 5–250) miles. The remaining 22 patients either had no associated transfer (transfer was canceled or patient improved while waiting for a bed), were mislabeled as AP but had other gastrointestinal or hepatobiliary problems, or had pancreatitis and/or complications related to a recent pancreatectomy. Patient characteristics of the 78 patients before transfer are listed in Table 1.

The initial admitting service was the surgical service in 38 patients (49%) and the medicine service in 40 patients (51%). During the course of the posttransfer hospitalization, six patients were subsequently transferred from the medical to the surgical service as follows: three patients who required operative intervention, two patients with interval computed tomography (CT) imaging that demonstrated progression of AP with necrosis, and one patient who had undergone a prior operation at the transferring facility and required further postoperative management. Seventeen patients (22%) were admitted directly to the intensive care unit.

3.2. Antibiotic usage pretransfer and posttransfer in AP

Pretransfer, abx were given to 51 patients (65%); in 78% of patients, the treatment consisted of multidrug coverage. Of the 78 total patients, at initial presentation at the index hospital (pretransfer) there were 5 patients that fell within the systemic inflammatory response syndrome (SIRS) criteria on admission (6%) and another 7 patients within the first 48 h (9%). Of these 12 patients total, there were three that resulted in documented indications for abx—bacteremia (1) and cholecystitis (2). The remainder of the nine patients that presented with SIRS criteria within 48 h of admission were placed on broad spectrum abx empirically for AP and therefore, in the absence of any other documented source of infection after initial work-up, should have been stopped. Within 24 h of arrival (posttransfer), abx were discontinued in 33 patients based on the absence of any documented infection or positive culture. Four patients were kept on abx for the presence of SIRS on arrival until further work-up was completed either documenting presence of absence of a source of infection. SIRS was defined as two or more of the following: temperature $\geq$38°C or <36°C; heart rate >90 beats per minute; respiratory rate >20 breaths per minute or partial pressure of arterial carbon dioxide <32 mm Hg; and white-cell count >12,000/mm^3 or <4000/mm^3 or the presence of more than 10% immature band forms [9]. Abx were started in six patients as follows: two patients with cholecystitis, two patients empirically for pancreatitis with fluid collections, and two patients empirically for gallstone pancreatitis (one with fever and history of bilateral lung transplant on immunosuppression). Antibiotic changes within the first 24 h of transfer are displayed in Table 2. Therefore, antibiotic use 24 h posttransfer was used in 24 patients total compared with 51 patient pretransfer (antibiotic use pretranfer *versus* posttransfer; 51 *versus* 24, $P < 0.001$). Empiric abx for AP without evidence of infection radiologically or by fine-needle aspirate

Table 1 – Characteristics of the transferred patients.

Variable	Total cohort, N = 78
Male:female ratio	38:40
Age, median (IQR)	50 (34–60)
BMI, median (IQR)	28 (24–31)
Previous admission for AP, *n* (%)	38 (49)
LOS before transfer (d), median (IQR)	6 (2–13)
ICU before transfer, *n* (%)	17 (22)
Etiology, *n* (%)	
Biliary	36 (46)
Idiopathic	16 (20.5)
Alcohol	13 (17)
Hypertriglyceridemia	9 (11.5)
Post-ERCP	2 (2.5)
Mass	1 (1.25)
Ampullary stenosis	1 (1.25)

BMI = body mass index; ERCP = endoscopic retrograde cholangiopancreatography; ICU = intensive care unit.

Table 2 – Antibiotic changes within the first 24 h of transfer.

Antibiotic indication	Pretransfer	Posttransfer	
	Pretransfer use, *n*	Posttransfer use, *n* (after those discontinued)	Posttransfer additional use, *n*
Positive blood culture	2	2	0
Positive urine culture	0	0	0
Dysuria (negative culture)	2	0	0
Cholecystitis	4	4	2
Choldeocholithiasis	2	0	2*
Cholangitis	0	0	0
Pancreatitis ± CT collection or necrosis	21	7	2
Pancreatitis ± leukocytosis or fever	15	0	0
SIRS	4	4	0
Pneumonia (CXR)	1	1	0
Pneumonia (respiratory culture)	0	0	0
Clostridium difficile	0	0	0
Subtotal	51	18	6
Total	51	24	

CXR = chest x-ray.
*Empirically started in one patient with transplant history on immunosuppression.

culture (but for presence of collections, necrosis, leukocytosis, or fever) was used in 36 patients pretransfer and decreased to nine patients posttransfer (empiric abx for AP pretransfer *versus* posttransfer, 36 *versus* 9, $P < 0.001$, Table 2). Of the nine patients posttransfer that were maintained or started on empiric abx for AP, seven patients were on a medical service and two patients were on a surgical service. Through the remainder of the posttransfer hospitalization, nine additional patients were placed on abx after the first 24 h. The indications for the abx were positive blood culture (1), positive urine culture (1), pneumonia with positive respiratory culture (2), Clostridium difficile infection (1), and drain and/or abscess culture (4).

3.3. *Nutrition in AP*

Fifty patients were fasted (nil per os [NPO]), and 19 patients were on total parenteral nutrition (TPN) at transfer to our institution, making up 89% of the cohort not on any type of enteral nutrition. This was reduced to 17% within 72 h after transfer by starting either an oral diet, postpyloric enteric tube feeds, or a combination of both (enteral nutrition pretransfer *versus* posttransfer, 9 *versus* 65, $P < 0.001$). The remaining 13 patients were advanced to enteral nutrition at a median of 7 d (IQR, 5–11). All surviving patients were discharged home on an oral diet, and six patients required supplemental nocturnal tube feeds for additional nutritional support.

3.4. *Timing of intervention in AP and clinical outcomes*

Fifteen patients were transferred for asymptomatic pseudocysts that were believed by transferring physicians to "require" drainage. On review of the associated CT or magnetic resonance imaging imaging, there were no cases that demonstrated presence of clinical or radiographic infection. Two of these patients had drains placed by interventional radiology before transfer that required upsizing and revision once they arrived at our institution (because once a drain is placed, we assume it has been iatrogenically contaminated and leave the drain). Of the remaining 13 patients with pseudocyst, five patients ultimately required intervention (two endoscopic cystogastrostomy with pigtail stent placement, two laparoscopic transgastric cystogastrostomy, and one open surgical cystogastrostomy). All five patients were treated beyond the early phase of AP (>4 wk), frequently being discharged and readmitted for intervention; the median time to intervention for the patients with pseudocysts was 86 d (40–93).

Five patients underwent operative debridement before transfer for pancreatic necrosis within the early phase, median time to operating room (OR), 11 d (IQR 9–21); all five of these patients required repeat intervention after transfer and all had prolonged length of stay (LOS, >21 d) after initial debridement (including pretransfer and posttransfer). Indications and outcomes of these five patients are listed in Table 3. Posttransfer, there were a total of 30 operative interventions; indications are listed in Table 4. Eight operative interventions for pancreatic necrosectomy were performed in the late phase of AP (>4 wk); median time to intervention was 44 d (IQR, 46–64). Again, patients were often discharged after initial transfer and readmitted for intervention as required

Table 3 – Indications and outcomes of patients that underwent early (< 4 wk) pancreatic debridement at the referring hospital (pretransfer).

Indication for debridement	Time to OR (d)	Infected	Pretransfer outcome	Posttransfer outcome	Postoperative LOS (d)*
Persistent pancreatic phlegmon	30	Yes, secondary to IR drain placement before OR	Respiratory failure and renal failure	Open necrosectomy, cholecystectomy, feeding jejunostomy, and tracheostomy	57
Persistent fluid collections despite IR drains	21	Yes, secondary to IR drain placement before OR	Pancreatic debridement five times with wound VAC closure, duodenal perforation, respiratory failure (trach), and renal failure (HD)	Laparoscopic pancreatic debridement, laparoscopic feeding jejunostomy, drains left for duodenal fistula control; persistent IR drain exchanges (1 y); open RNY HJ and GJ (2-y later)	52
Post-ERCP pancreatitis	11	No	Persistent fluid collections, multiple IR drains and ERCP stent	IR drain revisions; readmitted for MIRP two times	56
Hemorrhagic pancreatitis, abdominal compartment syndrome	9	No	Dilated small bowel, large open wound with VAC closure, renal failure (HD)	Abdominal closure	31
Phlegmon causing gastric outlet obstruction	8	No	Multiple drains, respiratory failure, and renal failure	Endoscopic cystogastrostomy; IR PTBD and gastrojejunostomy tube; ERCP/stent	109

ERCP = endoscopic retrograde cholangiopancreatography; GJ = gastrojejunostomy; HD = hemodialysis; HJ = hepaticojejunostomy; IR = Interventional Radiology; MIRP = minimally invasive retroperitoneal pancreatectomy; OR = operating room; PTBD = percutaneous transhepatic biliary drainage; RNY = Roux-en-Y; VAC = vacuum assisted closure.

*Postoperative LOS includes all time after procedure (postoperative stay at referring institution combined with postoperative stay at home institution).

Table 4 – Indications for operative intervention in the late phase (>4 wk) at home institution (posttransfer), $n = 30$.

Indication	Patients, *n*
Pseudocyst	3
Pancreatic redebridement (from pretransfer)	4
Pancreatic debridement (*de novo*)	8
Laparoscopic cholecystectomy	10
Other	
Internal hernia from previous Puestow PJ	1
Transduodenal pancreatic bx (AI pancreatitis), feeding jejunostomy	1
Laparoscopic cholecystectomy; bx gallbladder CA; hepatic resection 4b/5 and lymphadenectomy	1
Feeding jejunostomy, peritoneal fluid cytology	1
VATS for persistent pleural effusions after endoscopic cystogastrostomy and ERCP stent	1

AI = autoimmune; Bx = biopsy; CA = cancer; ERCP = endoscopic retrograde cholangiopancreatography; PJ = pancreaticojejunostomy; VATS = video-assisted thoracic surgery.

(median time to OR early *versus* late phase, 11 *versus* 46 d, $P = 0.043$). This delay in intervention led to a shorter postoperative LOS for the interventions performed >4 wk (postoperative LOS early *versus* late phase, 56 *versus* 16 d, $P < 0.05$).

3.5. *Postoperative mortality*

There were two 30-d deaths. One patient died because of pseudoaneurysm hemorrhage after pancreatic necrosectomy, which led to fatal bleed despite emergent Interventional Radiology (IR) intervention on postoperative day 12. The other patient was transferred for pancreatitis complicated by chronic superior mesenteric artery occlusion and pneumatosis. She was managed conservatively by the vascular service with aspirin until asymptomatic and discharged to a skilled nursing facility; however, she was reported to have died before her 3-wk follow-up appointment.

4. Discussion

AP is one of the most common gastrointestinal disorders requiring acute hospitalization worldwide with a reported annual incidence of 13–45 cases per 100,000 persons [10]. Mortality can be up to 30%–40% in severe cases. Such a common disease leading to 270,000 hospital admissions annually and inpatient costs exceeding 2.5 billion dollars [7,11] requires evidence-based treatment guidelines with broad support from the pancreatic community. Severe AP and the continuum of local pancreatic complications of AP extending from pseudocysts (fluid) to pancreatic necrosis (solid) are less common and clearly not divided into such discrete categories. The variability that exists in severe AP or necrotizing pancreatitis in terms of severity, timing of intervention, anatomic considerations, and accessibility of necrosis and/or collections remains very complex and is challenging to treat for those with less experience.

This study suggests that there is still great confusion in the treatment of both mild and severe AP in community hospitals. Even at our own institution, there is some discrepancy between disciplines (surgery *versus* hospitalist *versus* gastroenterology *versus* IR). Primary principles in the care of these patients are not routinely followed despite established guidelines, and very frequently, community caregivers resort to the historical dogmatic belief that AP is best treated with aggressive hydration, continuous fasting to "rest" the pancreas, and abx in efforts to "avoid" surgical intervention. The traditional management of infected necrosis has previously centered on open surgical debridement, often accompanied by significant risk of perioperative stress, organ failure, and long-term complications. Over the past decade, the treatment of severe AP and pancreatic necrosis has evolved substantially with improved critical care and nutrition management to facilitate supportive care in the early phase (<4 wk) and the introduction of a variety of minimally invasive modalities available for necrosectomy in the later phase (>4 wk) that have been used as alternatives to open surgery in critically ill patients [12–14]. These tools have helped modify the thinking that surgical intervention is not a "failure" of treatment but part of an ongoing strategy that follows appropriate medical management and optimization that are supported through these evidence-based practice guidelines for AP [15].

The paradigm shift and controversy over avoiding abx and encouraging enteral feeds has certainly centered on pancreatic necrosis. Infectious complications (pancreatic and extrapancreatic) are a major cause of morbidity and mortality in AP. When an infection is suspected, abx should be given while the source of infection is being investigated; however, once blood and other cultures are found to be negative and no source of infection is documented, abx should be discontinued. Although early unblinded trials suggested that administration of certain abx shown to penetrate pancreatic necrosis when given intravenously may prevent infections and/or complications in patients with sterile necrosis, subsequent, better designed randomized controlled trials have evaluated the use of prophylactic abx in severe AP and proved otherwise [16–18]. From a meta-analysis of the 11 best designed randomized controlled trials since 1993, routine use of prophylactic abx or use of abx in sterile necrosis is not recommended [19]. From our study, 36 patients at pretransfer with no infected necrosis (radiologically or by fine needle aspiration) were being treated with prophylactic abx. Ideally, all 36 cases of abx would have been discontinued but stopping abx all together in the setting of a "worsening" CT scan or increasing peripancreatic fluid collections can be challenging to adhere to. Within the first 24 h, this number was initially reduced to seven cases of prophylactic antibiotic for severe AP, but two more cases were added at transfer by the medical service. Of the nine cases of empiric antibiotic use, seven of these were maintained by the medical service and two cases were by the surgical service. These are likely small examples of local guideline dissemination as the surgical services (general surgery, acute care surgery, and surgical intensive care unit) are in closer contact with our hepatopancreatobiliary surgical service to know that these abx are not indicated. Eighty-nine percent of transferred patients were either fasted or on TPN. Most guidelines in the past recommended NPO until resolution of pain, and some even

suggested awaiting normalization of pancreatic enzymes before resuming oral feedings [1]. The assumption that the inflamed pancreas requires prolonged rest is not supported by laboratory and clinical investigation [20]; in fact, several studies showed that bowel rest is associated with mucosal atrophy and increased infectious complications. TPN also should be avoided in patients with mild and severe AP; multiple randomized trials have shown that TPN is associated with cholestasis and a dramatic increase in infectious complications [21]. Patients provided with oral feeding early in the course of AP very clearly have a shorter hospital stay, decreased infectious complications, decreased morbidity, and decreased mortality [20,22,23].

Fifteen patients were sent to us for assumed pseudocyst drainage. Asymptomatic, noninfected pseudocysts and pancreatic or peripancreatic necrosis do not warrant intervention regardless of size, location, or extension [7]. Best available evidence recommends surgical intervention be delayed until collections become walled-off, typically 4 wk after the onset of pancreatitis, in all patients with complications of necrosis [8,13]. All patients that were transferred to our institution that had undergone intervention in the early phase of AP at the referring institution required reintervention if not several interventions with a prolonged LOS. Delaying necrosectomy until 30 d after the initial admission is associated with decreased morbidity and mortality when compared with interventions in the first 2 wk [15]. That being said, despite purely knowing the "practice guideline" to wait at least 4 wk, there is still the challenge that exists to safely "delay intervention" and proceed with watchful waiting or temporizing measures to allow necrosis to be walled-off without exacerbating infection. Despite public, widespread dissemination of these guidelines, there is no optimal strategy to ensure good implementation of a guideline [24], and therefore, this issue remains problematic in centers without specifically experienced clinicians.

The limitations of this study include its small sample size and retrospective design. True severity scores are difficult to calculate based on limited consultation notes or transfer summaries alone. Probably the most reliable information came from the serial radiology images sent with each patient, but again, to rereview these images without complete clinical information to determine if an intervention could have been avoided is speculative at best. This study concept arose from the observation that many transferred patients with AP, even those that were considered more severe and associated with local complications of pseudocyst or mild necrosis improved quite rapidly by stopping excess treatment and allowing them to eat. It is possible that many of these referring institutions may be managing many cases of mild AP with good success and therefore, our view is biased by the more difficult cases that are being referred to our institution. However, H&P and admission notes from the index hospitalization at the outside hospital prior to transfer were reviewed, and only 12 patients (out of 78 total – 15%) fell within SIRS criteria within the first 48 h. Therefore, although a true denominator of all pancreatitis cases treated at the outside hospitals is unknown, the subset of patients transferred to our institution for further management comprised not only complicated cases but mild cases as well, with failure to follow best practice guidelines in both scenarios. It is our assumption that mismanagement of the more difficult and severe cases is truly an underlying misunderstanding of the same antiquated practices applied also to the less sick (mild cases of AP). For example, use of abx and NPO applied to a patient with mild AP (still a failure of best practice) is unlikely to have much clinical consequence—the patient with mild AP is anticipated to improve regardless if the practice guideline is followed or not. Consequently, the confusion arises in the community when the same therapies applied to cases of mild AP (historical, incorrect practice guidelines) are also applied to more severe cases of AP under the assumption that this strategy appeared to "work well" for the previous cases of mild AP. There is a failure to recognize that the consequences of additional abx and poor nutritional status will carry a much heavier weight in the overall care of the severe AP patient. Of course, those patients that were transferred and eventually required intervention did declare themselves, but all patients posttransfer were intervened on beyond the early acute phase and some were even followed as an outpatient before requiring further treatment (which often requires experience to be able to safely discharge these patients with close follow-up while waiting on the patient with "persistent unwellness" to declare necessity of intervention). Therefore, in managing patients with AP, the first element is implementing the basic practice guidelines to both mild and severe cases, but the second equally important element is that even following the guidelines to a tee often requires the assistance of multidisciplinary management with specialized expertise in the management of severe AP to achieve optimal outcomes.

5. Conclusions

In conclusion, evidence-based primary practice guidelines for the management of AP patients are widely available; however, the focus needs to shift to optimal dissemination and implementation of these guidelines to prevent lengthy hospitalizations and long-term morbidity of these complex patients. Several organizations have included postgraduate courses on the evolving management of AP—further studies involving pretests and posttests would provide meaningful data on baseline knowledge of these guidelines and how these educational programs can be most impactful. Ongoing efforts by pancreatologist specialists to use, present, and refer to these practice guidelines can increase awareness and optimize implementation of these guidelines so as to reduce variation in practice and improve patient outcomes.

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Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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