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ORIGINAL ARTICLE

Failure to follow evidence-based best practice guidelines in the treatment of severe acute pancreatitis

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Abstract

Objectives: Evidence-based guidelines for the treatment of severe acute pancreatitis have been established. This study was conducted to investigate the hypothesis that deviation from guidelines occurs frequently.

Methods: With institutional review board approval, the outside medical records of patients with severe pancreatitis who were transferred to the study institution during the period from July 2005 to May 2012 were reviewed. Severe pancreatitis was defined using the Atlanta Classification criteria. Records were reviewed with respect to published guidelines defining the appropriate use of imaging, antibiotics and nutritional support.

Results: A total of 538 patients with acute pancreatitis were identified. Of 67 patients with severe acute pancreatitis, 44 (66%) were male. The mean age of the patients was 55 years. Forty-five of 61 (74%) patients for whom relevant data were available were imaged upon admission, but only 15 (31%) patients were imaged appropriately by computerized tomography with i.v. contrast to assess the presence of necrosis or other complications. In patients for whom relevant data were available, prophylactic antibiotics were initiated in the absence of culture data or a specific infectious target in 26 (53%) patients. Total parenteral nutrition (TPN) was administered to 38 (60%) of 63 patients for whom relevant data were available; only 10 (17%) patients received enteric feeding. No nutritional support was provided to 15 (23%) patients.

Conclusions: Adherence to best practice guidelines in the treatment of severe pancreatitis is poor. The consistent application of current knowledge might improve outcomes in these patients.

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Introduction

Acute pancreatitis leads to approximately 210 000 hospital admissions each year in the USA. Fortunately, the majority of affected patients will experience rapid resolution of their symptoms with conservative treatment measures. However, a complicated clinical course ensues in approximately 25% of patients. Although the overall mortality rate in pancreatitis is only 5%, the presence of pancreatic necrosis and multi-system organ failure are associated with mortality rates of 17% and 47%, respectively.[1] Thus, patients destined to follow this severe clinical course must be identified early so that their nutritional support, risk for infection and any operative intervention can be managed appropriately.

To identify this subgroup of patients, a number of classification systems (APACHE II, Ranson, Glasgow, Balthazar, Atlanta[2]) have been developed based on objective clinical, biochemical and radiographic criteria. The Balthazar Classification scheme is image-based and utilizes contrast-enhanced computerized tomography (CT) obtained at 48–72 h after the onset of symptoms.

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Table 1 Summary of pertaining recommendations

Parameters	Recommendations[a]
Imaging	Perform contrast-enhanced computed tomography imaging 2–3 days after admission for the timely identification of pancreatic necrosis
Antibiotics	The use of prophylactic antibiotics is not recommended
Nutrition	For nutritional support, enteral nutrition should be used instead of total parenteral nutrition

[a]As outlined in Banks *et al*., 2006.[1]

This timeframe optimizes the ability to identify the absence or presence and extent of pancreatic necrosis. The extent of necrosis strongly correlates to the risk for subsequent infectious complications and thus an index CT demonstrating necrosis is of considerable clinical value.[3] The Atlanta Classification system also provides prognostic information and has been most widely utilized for clinical research. This system utilizes objective clinical data as inclusion criteria (Ranson score of >3 or APACHE II score of >8) and defines severe acute pancreatitis (SAP) as being associated with local and/or systemic complications.[2] One limitation of this system is that it actually identifies a diverse population of patients,[4–7] but a recently published revision[5] now subdivides this into patients with moderately severe[5–7] and critically severe categories of disease.[8,9] The updated Atlanta Classification achieves this additional level of stratification by differentiating between local and systemic complications, their timing and duration.[5] Together, these classification systems facilitate the identification of at-risk patients and subsequent management decisions on their need for critical care, nutritional support and surgical intervention.

An extensive literature has identified the interventions that provide the best outcomes for patients with SAP and represents the basis of published, best practice treatment guidelines.[1,10–15] These recommendations address the timing and modality of imaging, the use of prophylactic antibiotics, and the introduction and modality of nutritional support (Table 1). These data also provide guidance for other interventions, including endoscopic retrograde cholangiopancreatography (ERCP) percutaneous drainage or other operative procedures, but these recommendations are not as broadly applicable. Poor adherence to these recommendations has been reported in the UK, Western Europe and New Zealand,[16–20] although recent audits suggest compliance has been improving.[21,22] Surprisingly, data from the USA are lacking. Thus, adherence to best practice guidelines for the treatment of SAP amongst physicians in the southeastern USA was assessed. It was hypothesized that adherence to these guidelines is poor.

Materials and methods

Following institutional review board approval, medical records were obtained for all patients admitted to the University of Florida and Shands Teaching Hospital (UF & Shands) with the primary diagnosis of acute pancreatitis [International Classification of Diseases, 9th Revision (ICD-9) code 577.0] between July 2005 and May 2012. Patients under the age of 18 years at the time of diagnosis and patients who were directly admitted to the study institution were excluded.

Patients without SAP were excluded. The designation of SAP was based on the Atlanta Classification.[2] Thus, any patient with acute pancreatitis and either organ failure or local complications was included. Organ failure was defined as any of the following: shock [systolic blood pressure of <90 mmHg, pulmonary insufficiency indicated by an arterial blood oxygen pressure (PaO_2) of <60 mmHg as measured on room air or need for ventilator support]; renal failure (creatinine of >2 mg/dl following rehydration or need for renal replacement therapy); disseminated intravascular coagulation (platelet count of <100 000/μl and fibrinogen of <1 g/l), and metabolic disturbances (calcium level of <7.5 mg/dl). Local complications included acute fluid collections, pancreatic necrosis, pseudocyst formation and pancreatic abscess. Patients presenting with a Ranson score of ≥3 calculated within 48 h of admission to the referring institution were also included.

Following the identification of patients with SAP transferred from outside institutions, outside and institutional medical records were retrospectively reviewed for each patient. Records reviewed included admission and progress notes, radiology reports, laboratory test values, procedural notes and nursing notes. Patients for whom available records were inadequate to assess at least two items of interest were excluded from further review. The calculation of any given outcome measure was based on data for only those patients whose records for that variable were clear and complete. Thus, although the total number of patients is 67, an outcome measure may refer to fewer than 67 patients because of incomplete transfer records. Actual treatment patterns were compared with best practice standard guidelines with respect to the use and timing of appropriate imaging (contrast-enhanced CT), the use and spectrum of antibiotics, and the timing of the initiation and the modality of nutritional support.[1]

Results

Clinical characteristics of the patient population

Of 538 patients admitted with acute pancreatitis, 67 met the study inclusion criteria. The clinical characteristics of the cohort are summarized in Table 2. These patients were transferred from 38 different hospitals in Florida. The mean ± standard deviation (SD) length of stay at the referring institution prior to transfer was 13.7 ± 12.4 days (range: 1–56 days; median: 11.0 days). 54% of patients required intensive care for at least a portion of their stay prior to transfer. The mean ± SD Ranson score at the time of the initial hospital admission was 3.3 ± 1.8 (range: 1–8; median: 3.0). Following transfer, the median hospital stay was 29.0 days. Six (9%) patients died following transfer.

Thirty-five (52%) patients had biliary pancreatitis (Table 3). Alcohol abuse was the aetiology in 18% of cases. Post-ERCP pan-

Table 2 Patient demographics

Parameters	Value
Patients, *n*	67
Age, years, mean (range)	55 (18–78)
Sex, %	
Male	44 (66%)
Female	23 (34%)
Body mass index, kg/m^2, mean (range)	30 (17–43)
Comorbidities, *n* (%)	
Coronary artery disease	20 (30%)
Diabetes mellitus	20 (30%)
Hypertension	42 (63%)
COPD/active smoking	21 (31%)
Alcohol abuse	11 (16%)
Chronic renal insufficiency	4 (6%)
CVOD (TIA, stroke, CEA)	5 (8%)
Dyslipidaemia	22 (33%)
Ranson score[a], median (range)	3.0 (1–8)
LoS at referring institution, days, median (range)	11.0 (1–56)
Patients admitted to ICU at referring institution, *n* (%)	33 (54%)
LoS at UF & Shands Hospital, days, median (range)	29.0 (1–182)

[a]As calculated based on parameters measured within the first 48 h of admission at the referring institution.
COPD, chronic obstructive pulmonary disease; CVOD, cerebral vascular occlusive disease; TIA, transient ischaemic attack; CEA, carotid endarterectomy; LoS, length of stay, UF & Shands, University of Florida and Shands Teaching Hospital.

Table 3 Disease-specific details[a]

Parameter	*n* (%)
Local complications	
Necrotizing pancreatitis	31 (47%)
Infection	14 (21%)
Pseudocyst	23 (35%)
Multi-organ failure	24 (38%)
Procedures	
Surgical	7 (11%)
Interventional radiology	18 (28%)
ERCP	8 (12%)

[a]Diagnoses and interventions as established or performed during the patient's stay at the outside institution.
ERCP, endoscopic retrograde cholangiopancreatography.

creatitis was present in three (4%) patients, hyperlipidaemia in four (6%), pancreas divisum in one (1.5%) and pancreatic head mass in one (1.5%). Two cases (3%) were likely to have been induced by medications, and 10 (15%) had no clearly identifiable cause.

Assessment of adherence to best practice guidelines

Forty-five of 61 (74%) patients with adequate documentation for assessment underwent abdominal imaging upon admission (within 24 h) (Table 4). Of these patients, 40 (66%) underwent CT. Fifteen (25%) patients underwent their first radiological imaging after the initial evaluation (>24 h). This occurred at an average of 3.1 days (range: 1–7 days) post-admission. One individual was not imaged at the referring institution and was transferred <48 h after admission. The initial mode of abdominal imaging was a CT with i.v. contrast in 72% of patients, CT without contrast in 18%, and ultrasound examination alone in 8%. Of the patients who stayed beyond 48 h at the referring hospital, 15 (31%) underwent a CT with i.v. contrast at 48–72 h. This subgroup includes patients who underwent a repeat CT in addition to CT at admission and patients who were not imaged by CT upon admission.

Table 4 Practice guideline adherence details

Parameter	Value
Modality of initial imaging, *n* (%)	
CT with i.v. contrast	43 (72%)
CT without i.v. contrast	11 (18%)
Abdominal ultrasound	5 (8%)
No abdominal radiological imaging	1 (1.5%)
Timing of CT imaging, *n* (%)	
At time of admission[a]	40 (66%)
After admission	15 (25%)
Time from admission, days, mean (range)	3.1 (1–7)
CT with i.v. contrast at 48–72 h, *n* (%)	15 (31%)
Antibiotic use, *n* (%)	51 (79%)
Prophylactic use[b]	26 (53%)
Carbapenem antibiotics	11 (42%)
Non-carbapenem antibiotics	15 (58%)
Nutrition	
Time without nutrition[c], days, mean (range)	2.6 (0–7)
Enteral feeding, *n* (%)	10 (17%)
TPN administration, *n* (%)	38 (60%)
Enteral or oral feeding used or considered first, *n* (%)	7 (23%)
Albumin[d], g/dl, mean (range)	2.6 (1.8–4.1)

[a]Within first 24 h, as part of admission investigative process.
[b]Antibiotics initiated in the context of leukocytosis and/or fever, with no specific infective process targeted.
[c]Time until commencement of either artificial nutrition or oral diet as calculated from time of admission.
[d]As measured upon admission to University of Florida and Shands Teaching Hospital.
CT, computed tomography; TPN, total parenteral nutrition.

A total of 51 patients (79%) received antibiotic treatment during their pre-transfer stay; for 26 (53%) of these patients, treatment was empiric and did not target a specific infection source. Of the patients who were prescribed prophylactic treatment, 11 (42%) received carbapenems and the remaining 15 (58%) patients were given other antibiotics. Seven patients received imipenem or imipenem and cilastatin, and four patients

were prescribed meropenem. For patients who did not receive carbapenems, the most common prophylactic antibiotics were vancomycin ($n = 7$), metronidazole ($n = 7$), levofloxacin ($n = 5$), piperacillin-tazobactam ($n = 4$) and cefepime ($n = 3$).

Sixty of the 64 (94%) patients for whom adequate nutrition records were available were fasted at the time of admission; four (6%) were allowed to continue an oral diet. Patients were maintained without any nutritional support for a mean ± SD period of 2.6 ± 2.1 days (range: 0–7 days). Ten (17%) patients received enteral nutrition via a nasoenteric or percutaneous endoscopic gastrostomy (PEG) tube, and 38 (60%) received total parenteral nutrition (TPN). The latter was started at a mean of 3.8 days (range 0–23 days), and enteral feeding was started at a mean of 2.0 days (range: 0–4 days). For the subset of patients who were nourished parenterally, seven of 31 made an initial attempt to feed orally or enterally. Causes for switching to TPN in these patients included intolerance of oral diet ($n = 4$), inability to place a nasoenteric feeding tube ($n = 1$) and intolerance of tube feeding ($n = 2$). Fifteen (23%) patients did not receive any nutritional support. The median stay at the outside institution in patients who received no nutritional support was 3 days (range: 1–13 days). Mean ± SD albumin in the entire cohort was 2.6 ± 0.6 g/dl (range: 1.6–4.1 g/dl).

Upon transfer, 40 (60%) patients underwent a new CT with i.v. contrast within 24 h of admission. Two (3%) patients underwent CT without i.v. contrast on the basis of renal impairment, and 25 (37%) patients were deemed to have had adequate recent imaging performed at the outside institution. Of the 26 patients who received prophylactic antibiotics at the outside institution, 25 were still being treated upon transfer to the study hospital. Within 48 h of arrival, antibiotics were discontinued in seven of these patients, therapy was continued on a prophylactic basis in eight patients, and antibiotic therapy was continued in order to appropriately treat a culture-proven infection in 10 patients. Of the 38 patients who arrived on TPN, 29 were converted to enteral nutrition, eight were continued on TPN, and one patient died shortly after transfer.

Discussion

The present study found that, in general, the treatment of patients with SAP prior to transfer failed to adhere to evidence-based best practice guidelines. Computed tomography imaging was inappropriately utilized with respect to timing and the use of i.v. contrast. Prophylactic antibiotic usage was widespread but infrequently included a carbepenem. Nutritional support was initiated in a timely fashion; however, most patients received TPN and few received enteral nutrition.

Best practice guidelines for the treatment of patients with severe pancreatitis were published by Banks *et al.*[1] in 2006, and were based on evidence published prior to the start of the period covered in the present study (in 2005). These guidelines recommend imaging with contrast-enhanced CT at 48–72 h post-admission to delineate local complications and the presence and extent of necrosis. This time interval has been identified as the optimum period in which to detect the complication of pancreatic necrosis.[3,5] Morphological findings on CT at the time of admission were found to have poor predictive value and thus its use as a triage tool is not recommended.[23] A large proportion of patients in the present study (66%) underwent CT within 24 h of admission, but only 31% of patients were imaged with contrast-enhanced CT at 48–72 h. Thus, although CT as part of the initial diagnostic evaluation of severe abdominal pain may be appropriate, the majority of these patients did not benefit from the properly timed imaging essential to treat them appropriately.

The occurrence of infection in the pancreatic field sharply increases mortality,[1] and the revised Atlanta Classification acknowledges that mortality increases further in the presence of persistent organ failure.[5] The use of prophylactic antibiotics in severe pancreatitis is controversial and this controversy persisted during the period of this study.[24–28] Some studies have shown evidence supporting the use of prophylactic imipenem in severe pancreatitis,[24,29,30] whereas others have found no benefit.[31,32] A 2010 meta-analysis by Villatoro *et al.* found a statistically significant improvement in the rate of pancreatic infections following treatment with imipenem, but no difference in mortality.[33] This runs counter to the findings of Wittau *et al.*, who specifically analysed carbapenem prophylaxis in a separate meta-analysis and found no benefit.[34] This difference in findings can be attributed in part to the fact that two additional trials that failed to show added benefit with prophylactic imipenem treatment[31,32] were included in the study by Wittau *et al.*[34] The most recent meta-analysis on the subject, by Wittau *et al.*, found no reduction in mortality pancreatic and non-pancreatic infections with the use of antibiotic prophylaxis.[34] Given that this practice is associated with an increased risk for pancreatic fungal infections[35–37] and increased antibiotic resistance,[38] it has been further discouraged. The present study found that a large proportion of the patient population (53%) had been prescribed antibiotics for the clinical features of a systemic inflammatory response in the absence of a specifically targeted infective source. Although it might be useful to apply the benefit of doubt for the use of imipenem, given the ongoing debate regarding its prophylactic benefit, more than half of the present cohort (58%) were given non-carbapenem antibiotics.

Nutritional support is an important component of the management of SAP. Multiple randomized trials have demonstrated that enteral feeding is associated with better outcomes than TPN.[1,39–41] A recent meta-analysis has shown statistically significant decreases in risk for infectious complications and mortality with the use of enteral rather than parenteral feeding.[40] Despite this, the use of TPN remains pervasive in both the present study population and in the previously published literature.[21,42] In the present series, the mean time of commencement of nutritional supplementation was day 2.0 for enteral feeding and day 3.8 for TPN. This is in concurrence with recommendations that nutritional supplementation be started early in the disease process.[1]

However, recent evidence suggests that if parenteral nutrition must be used, it should not be administered until day 5 because the early employment of TPN (within 48 h) has been associated with worse outcomes.[43] Twelve of the 38 patients who received TPN in the present study were set on this route by day 3 of their hospital stay.

The present findings are similar to those reported in a number of publications from outside the USA. One recent practitioner questionnaire-based study by Rebours *et al*. looked at similar variables in France.[21] These investigators found suboptimal adherence to SAP treatment guidelines across a large number of public and private institutions surveyed in 2008, although their findings indicated an improvement in compliance compared with a previous survey conducted in 2001.[21] Specifically, the use of prophylactic antibiotics was found to be low at 8%,[21] which is much lower than the rate of 53% observed in the present study. Similarly, CTs were performed at the time of admission in 28% of patients and at 48 h in 69%, whereas the present study found rates of 66% and 31%, respectively, at these time-points. Rebours *et al.* [21] reported that parenteral nutrition was employed in 42% of patients, whereas enteral nutrition was used in 58%. A 2007 prospective observational study assessing compliance in Italian centres found parenteral nutrition was administered in 89% of patients, whereas enteral nutrition was applied in only 5%.[19] This highlights the heterogeneity of practice patterns across the world. Thus, failure to adhere to best practice guidelines is not unique to the US health system.

The present study has a number of limitations. It is retrospective in nature and was compelled to exclude a significant number of patients because adequate documentation was lacking. In addition, it should be acknowledged that charted notes often do not effectively communicate clinical thought processes. Another limitation concerns the fact that the present study assessed care provided at only community hospitals in Florida. It is very possible that clinical practice patterns differ at large academic centres and elsewhere in the USA. Thus, the present findings should not be considered as representative of treatment patterns at state or national levels.

Failure to apply best practice guidelines is not unique to the context of severe pancreatitis and remains an unresolved challenge. Nonetheless, opportunities for improvement in the knowledge of and adherence to these guidelines certainly exist. Assuming culpability for the present data, the current authors have begun a regional outreach effort to improve the knowledge of emergency department and intensive care unit physicians of the identification of severe pancreatitis and optimum subsequent treatment. Subspecialty organizations, such as the Americas Hepato-Pancreato-Biliary Association (AHPBA) and other societies, could develop continuing medical education resources and other outreach strategies targeting community-based physicians. Perhaps this might include contributions to widely disseminated publications. Outwith physician influence, compliance with these guidelines might be tied to reimbursement, as has applied with other best practices through the Centers for Medicare and Medicaid Services (CMS) core measures programme.

Conflicts of interest

None declared.

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