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Original article

Management and outcomes of acute pancreatitis patients over the last decade: A US tertiary-center experience

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ABSTRACT

Background/objectives: Acute pancreatitis (AP) management remains largely supportive and can be challenging in patients with severe disease. This study aims to describe a ten-year US tertiary-center experience in managing AP patients.
Methods: Clinical management and outcomes of 400 prospectively enrolled AP patients stratified by the Revised Atlanta Classification were analyzed; trends in management between early (2004–2008) and late enrollment phase (2009–2014) were assessed.
Results: Fifty-two% of patients were classified as mild AP (MAP); moderately severe (MoAP) and severe (SAP) grades contained 23.5% and 24.5% of participants. Intravenous fluid administration during the first 24 h (MAP 3.7, MoAP 4.7, and SAP 4.8 L), need for ICU (6%, 23%, 93%), and nutritional support (7%, 51%, 90%) increased significantly with greater AP severity ($p < 0.001$). One hundred fifty five (39%) patients developed necrotizing AP, of which 41% received prophylactic antibiotics, and 44% underwent pancreatic drainage/debridement. Prophylactic antibiotics (58% vs. 27%) and interventions (63% vs. 27%) were noted more frequently in SAP than MoAP ($p < 0.001$). Enteral nutrition (18% vs. 30%) and minimally invasive pancreatic interventions (19% vs. 41%) were more commonly used in the late phase ($p < 0.05$). The overall median length of hospitalization was 7 days reaching 29 days in SAP group. Mortality was 5%; all deaths occurred in SAP group.
Conclusions: This study provides an extensive report on clinical management of AP and its trends overtime. Pancreatic intervention is required in less than 50% of patients with necrotizing pancreatitis. Utilization of enteral nutrition and minimally invasive pancreatic interventions has been increasing over time.
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1. Introduction

Acute pancreatitis (AP) is an inflammatory process of the pancreas characterized by sudden onset and highly variable clinical course. With 270,000 annual admissions in the United States, AP is the leading gastrointestinal-related reason that people enter the hospital [1]. The economic burden of AP exceeds 2.5 billion US dollars per year [2,3]. Most AP patients have a mild disease course with focal interstitial inflammation of the pancreatic parenchyma and rapid restoration of homeostasis. However, about 20% of individuals who experience an episode of AP develop systemic inflammatory response syndrome (SIRS) and subsequent organ dysfunction. This group of AP patients typically requires intensive care unit (ICU) management, prolonged hospitalization, and has a mortality rate as high as 30% [4].

Recent advances have been made in classifying the severity of AP. After an extended period of expert discussion, two updated classification systems were published: the Revised Atlanta (RAC) [5], and the Determinant-based Classification of Severity [6]. The

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RAC categorizes AP patients as mild, moderate, or severe and the DBC stratifies them to 4 groups: mild, moderate, severe and critical, based on various clinical parameters. Very few studies have compared clinical outcomes in AP patients by RAC and/or DBC severity grades [7–9]. Nonetheless, there is paucity of empiric data on management of AP patients grouped according to the RAC/DBC.

The goal of our study is to examine numerous aspects of management and clinical outcomes in a sizable, prospectively-enrolled cohort of AP patients from a U.S. tertiary center that are categorized according to the RAC. Based on the assessment of our cohort, we will describe management trends of AP over the last decade.

2. Methods

2.1. Study design and patients

The Severity of Acute Pancreatitis/Pancreatitis-associated Risk Of Organ Failure (SAPS/PROOF) is an observational cohort study conducted at the University of Pittsburgh Medical Center (UPMC) that aims to assess risks, biomarkers, and outcomes in AP [10,11]. Patients have been prospectively enrolled in two chronological phases. The first phase began in 2004 and lasted until early 2008. The second phase began in 2009 and remains ongoing. Patients included in this report were enrolled until 2014. The Institutional Review Board at the University of Pittsburgh approved the study protocol (IRB protocol ID PRO08010374). All participants signed a written informed consent form prior to enrollment. For seriously ill patients unable to provide consent, the next of keen was contacted. At a later point, when patients' clinical condition improved, they were also informed about the study and signed informed consent. Only AP patients captured relatively early in the disease course (within 72 h from onset) were included in the study. Based on our retrospective review of electronic medical records, approximately 45% of all AP patients admitted or transferred to our institution were enrolled in the study. The percentage of AP patients requiring ICU admission was similar between all comers and our prospective enrolled cohort.

At the time of patient enrollment, detailed questionnaires on demographics and clinical characteristics were collected. Close monitoring of the clinical course including laboratory and imaging tests, therapeutic approaches and disease outcomes were recorded on a prospective daily basis for the first week and then weekly in case of prolonged hospitalization. Therefore, in the present report data on demographics, laboratory measurements, clinical course, management therapies, and outcomes were all abstracted prospectively. Detailed data on specific parameters of treatment required for this manuscript, such as the volume of intravenous fluid (IVF) administered, prophylactic antibiotics, and interventions for walled-off necrosis (WON), were retrospectively collected from electronic medical record review by participating physicians. The major criterion for transferring AP patients to our institution was the development of moderately severe or severe disease. For patients with mild AP the two main etiologies for transfers were need for ERCP or nutritional support. Outside hospital medical records of patients transferred to our institution were retrieved and reviewed. For all transferred patients, disease onset was considered the original presentation at the outside hospital.

RAC was utilized because it focuses on the early, dynamic nature of AP compared to DBC [8]. Study patients were retrospectively assigned a severity grade based on the RAC system [5].

2.2. Computerized tomography

Contrast-enhanced computerized tomography (CECT) scans were performed upon the discretion of the primary treatment team. Initial and follow-up CECT scans were reviewed retrospectively by two abdominal radiologists with subspecialty training (AD, AF), who were blinded to patients' outcomes. RAC definitions were used for local complications [5].

2.3. Definitions

The diagnosis of AP was defined as the presence of at least two of the three following criteria: 1) Epigastric abdominal pain that is typical of AP, 2) Serum amylase or lipase elevated to greater than three times the upper limit of normal, and/or 3) CT scan (or less commonly magnetic resonance imaging [MRI]) findings consistent with AP [12].

Organ failure was defined using the modified Marshall scoring system involving cardiovascular (systolic blood pressure <90, not fluid responsive, or pH < 7.3), respiratory (PaO_2 mmHg/FiO_2<300), or renal system derangements (serum creatinine >1.8 mg/dL) [5]. Single organ failure was determined by the involvement of a single system, whereas multiple organ failure was designated by the presence of organ failure in two or more systems [5]. Transient organ failure was assigned to duration of less than 48 h, while persistent organ failure was described if organ failure lasted longer than 48 h.

Local complications were defined using RAC terminology [5]. AP was morphologically classified as 'interstitial' when only pancreatic edema and/or peripancreatic stranding were present. AP was categorized as 'necrotizing' when parenchymal and/or peripancreatic tissue necrosis developed. Pancreatic necrosis was determined by the lack of pancreatic gland enhancement on CECT scan or by direct identification of necrosis upon laparotomy. Peripancreatic necrosis was defined by the presence of heterogeneous areas of non-enhancement on CECT scan that contain non-liquefied, ill-defined components, nodular areas of increased peripancreatic fat attenuation with visual density higher than simple fluid and considerably higher than simple stranding without pancreatic necrosis. Infected necrosis was diagnosed by the presence of extraluminal gas in the pancreatic or peripancreatic tissues on CECT scan, or by positive Gram staining and/or cultures after fine-needle aspiration or necrosis debridement [13]. Extrapancreatic infections included bacteremia, sepsis of unknown origin, and *Clostridium difficile* colitis, as well as respiratory, urinary, or biliary tract infections. These infections developed during hospitalization and were diagnosed based on a combination of clinical symptoms, imaging studies, and laboratory tests (e.g. blood and/or urine cultures, stool *Clostridium difficile* toxin testing).

Severe AP (SAP) based on RAC was defined as persistent organ failure in one or more physiologic systems [14,15]. Moderately severe disease (MoAP) included a mixed group of the following criteria: transient organ failure, exacerbation of baseline comorbidities, and/or local complications including pancreatic and peripancreatic necrosis. It is important to mention that necrosis, sterile or infected, in the absence of persistent organ failure was classified as MoAP according to RAC. Thus, patients with infected pancreatic necrosis and no organ failure were classified as MoAP. Mild AP (MAP) was selected by the absence of any systemic or local complications.

The SIRS score and serum blood urea nitrogen (BUN) levels were recorded on admission and at 48 h. The SIRS score was calculated based on the presence of the following criteria: 1) temperature above 38C° (100.4 °F) or below 36 °C (96.8 °F), 2) heart rate greater than 90 beats per minute, 3) respiratory rate higher than 20 breaths per minute or PaCO2 less than or equal to 32 mm Hg or ventilator use, and 4) white blood cell (WBC) count higher than 12,000/μL or lower than 4000/μL or the presence of over 10% immature (band)

forms [16]. A positive SIRS score was defined as the presence of 2 or more of these criteria.

2.4. Management and outcomes

In terms of management, the following factors were reviewed for each patient: IVF administration during the first 24 h in patients directly admitted to UPMC facilities, ICU admission, ICU length of stay, nutritional support, interventions for necrotizing AP, urgent (within 48 h) and non-urgent ERCP, cholecystectomy, plasmapheresis for hypertriglyceridemia-induced AP, and hemodialysis for persistent renal failure. Use of prophylactic antibiotics, specifically carbapenem, in patients with necrotizing pancreatitis without signs of systemic infection was also recorded.

Admission in the ICU at our institution was based on clinical judgment. Patients at risk for developing severe AP, i.e. with APACHE II score >8 in the first 24 h of admission or persistent SIRS, were also admitted to the ICU for close monitoring.

Interventions for necrotizing AP included open surgery or minimally invasive approaches such as laparoscopic necrosectomy, percutaneous drainage catheter placement, and endoscopic drainage (cystenterostomy), or debridement (direct endoscopic necrosectomy). Patients with necrotizing AP were followed for at least 9 months after study enrollment in order to capture those patients who required intervention.

Hospital length of stay included the duration of outside hospitalization for patients who were transferred into our care. Mortality was defined as death during hospitalization or up to 10 days following hospital discharge.

We grouped patients in two time frames targeting similar duration of enrollment that would provide close to 200 patients per group. The first group (early phase) included patients enrolled at any point between 2004 and 2008 (n = 191) and the second group (late phase) were those who joined the study between 2009 and 2014 (n = 209).

An expert committee was formed at the University of Pittsburgh in 2013 aiming to develop institutional guidelines for the management of AP, entitled Acute Pancreatitis PowerPlan. Prior to 2013, physicians taking care of AP patients followed the published gastroenterology association guidelines. A joint medical-surgical conference is held every week, where all complex pancreatic cases are discussed and consensus decisions are made in regards with their management. Patients with predicted mild AP are admitted under the medical service; whereas, patients with impeding organ failure or complicated transfers from outside hospitals are admitted under the surgical service. Urgent ERCP is performed in AP patients with established or suspected concomitant cholangitis. Institutional policy is to perform laparoscopic cholecystectomy during index hospitalization in patients with mild AP.

2.5. Statistics

Continuous data were evaluated for normality of distribution by the Kolmogorov-Smirnov test. Normally distributed data are presented as mean values ± standard deviation (SD), whereas data that are not normally distributed are shown as median values with interquartile range (IQR). Differences between two groups with continuous data were assessed using the student-t test for normally distributed data and the Mann-Whitney test for non-normal data distributions. Comparisons of three groups of data were made using one-way analysis of variance (ANOVA) and Kruskal-Wallis (non-parametric ANOVA) tests. Discrete data were compared by the chi-square or chi-square trend test depending on the number of groups. A two-sided p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using STATA 13 (StataCorp, College Station, TX). No power calculations were performed before undertaking statistical analysis. The decision to analyze our results, when we reached enrollment of 400 patients, was arbitrary.

3. Results

3.1. Patient demographics

A total of 400 patients with AP were recruited into the study. The mean age of participants was 52 years (SD ± 19). Two hundred and six patients (52%) were male and 363 (91%) were white. Median body mass index (BMI) was 28 kg/m^2 (IQR 25, 33) with 160 patients (40%) being obese (BMI ≥30). Biliary was the most common etiology of pancreatitis, identified in 155 patients (39%), followed by idiopathic AP (20%), post-ERCP AP (14%), alcoholic AP (14%), and hypertriglyceridemia-induced AP (7%). Of the 400 enrolled patients, 217 (54%) were transferred from an outside hospital to our tertiary center early in their disease course. This was the first (sentinel) episode of AP for 269 patients (67%). One hundred and forty five patients (38%) had SIRS on admission. The median serum BUN on admission was 14 mg/dL (10, 22; Table 1).

3.2. The RAC grades

Based on the RAC, two hundred and eight patients (52%) were categorized as having MAP, 94 (23.5%) as MoAP, and 98 (24.5%) as SAP. The MoAP grade included three subsets of patients: 82 patients with necrotizing AP (61 with pancreatic and 21 with isolated peripancreatic necrosis), 6 who developed transient organ failure without local complications, and 6 with exacerbation of underlying comorbidities (2 with congestive heart failure, 2 with diabetic ketoacidosis, 1 with COPD, and 1 with renal transplant rejection; Fig. 1).

In the SAP grade, multisystem organ failure was observed in 59 of 98 patients (60%). The organ system most commonly afflicted was the respiratory (n = 79) system, followed by the renal (n = 73) and cardiovascular (n = 37) systems. The majority of patients developed organ failure within the first 48 h of initial admission (70, 71%), while 22/98 (22%) had organ failure at presentation to the hospital (UPMC or outside hospital). Another 18 participants developed organ failure within day 3–7. Only 5 SAP patients were diagnosed with organ failure between the 1st and 2nd weeks and 5 SAP patients developed organ failure after 2 weeks. Out of 98 SAP patients, 73 were diagnosed with concomitant necrotizing AP (pancreatic necrosis in 63 and peripancreatic necrosis in 10 patients).

When demographics between the severity groups were compared, no significant differences in mean age or race were identified (Table 1). The ratio of male to total patients increased from MAP to MoAP and SAP grades, reaching 66/98 (67%) patients in the latter. Subjects with more severe disease were significantly more likely to be obese than those with milder disease; 60% of SAP patients had a BMI in the obese range. In respect to etiology, alcoholic and hypertriglyceridemia-induced AP were more commonly seen in MoAP (18% and 11%) and SAP (18% and 12%) grades when compared to MAP (9% and 3%, respectively; $p \leq 0.03$). Post-ERCP AP was rarely an etiology that resulted in severe disease, noted in only 4 of the 98 patients in the SAP grade. The majority of MoAP (61%) and SAP patients (85%) were transferred from outside facilities. Patients with their first attack of AP developed higher rates of severe disease (81/269; 30%) when compared to patients with recurrent attacks (17/131; 13%; $p < 0.001$).

In respect to risk stratification, SIRS was observed more frequently with increasing severity grades reaching 60/93 (65%) at

Table 1
Demographics, etiologies, and severity predictors in our cohort categorized by the Revised Atlanta Classification.

	All AP n = 400	MAP n = 208 (52%)	MoAP n = 94 (23.5%)	SAP n = 98 (24.5%)	p-value
Age, mean ± SD	52 ± 19	51 ± 19	51 ± 19	54 ± 17	0.3
Gender (male; %)	206 (52)	89 (43)	51 (54)	66 (67)	<0.001
Race (white; %)	363 (91)	184 (88)	90 (96)	89 (91)	0.13
BMI, median (IQR)	28 (25,33)	27 (24,32)	28 (24,33)	31 (28,35)	<0.001
Obesity (BMI≥30; %)	160 (40)	68 (33)	33 (35)	59 (60)	<0.001
Transfers (%)	217 (54)	77 (37)	57 (61)	83 (85)	<0.001
Sentinel AP (%)	269 (67)	133 (64)	55 (59)	81 (83)	0.001
Etiology					
▪ Biliary (%)	155 (39)	82 (39)	29 (31)	44 (45)	0.13
▪ Alcoholic (%)	54 (14)	19 (9)	17 (18)	18 (18)	0.03
▪ Idiopathic (%)	78 (20)	43 (21)	22 (23)	13 (13)	0.17
▪ Hyperthiglyceridemic (%)	28 (7)	6 (3)	10 (11)	12 (12)	0.002
▪ Post-ERCP (%)	55 (14)	40 (19)	11 (12)	4 (4)	0.001
▪ Other (%)	30 (7)	18 (9)	5 (5)	7 (7)	0.63
SIRS on admission (%)[a]	145/383 (38)	44/205 (21)	41/85 (48)	60/93 (65)	<0.001
SIRS at 48 h (%)[a]	132/356 (37)	30/186 (16)	32/79 (41)	70/91 (77)	<0.001
BUN on admission, median (mg/dL; IQR)	14 (10, 22)	12 (9, 20)	13 (9, 18)	21 (13, 35)	<0.001
BUN at 48 h, median (mg/dL; IQR)	10 (6, 22)	8 (5, 13)	8 (6, 15)	36 (20, 52)	<0.001

AP: acute pancreatitis; MAP: mild acute pancreatitis; MoAP: moderately severe acute pancreatitis; SAP: severe acute pancreatitis; SD: standard deviation; IQR: interquartile range; ERCP: endoscopic retrograde cholangiopancreatography; SIRS: systemic inflammatory response syndrome; BUN: blood urea nitrogen.
p-values represent trend test comparisons between MAP, MoAP, and SAP grades.
[a] Denominators reflect number of patients with available SIRS scores.

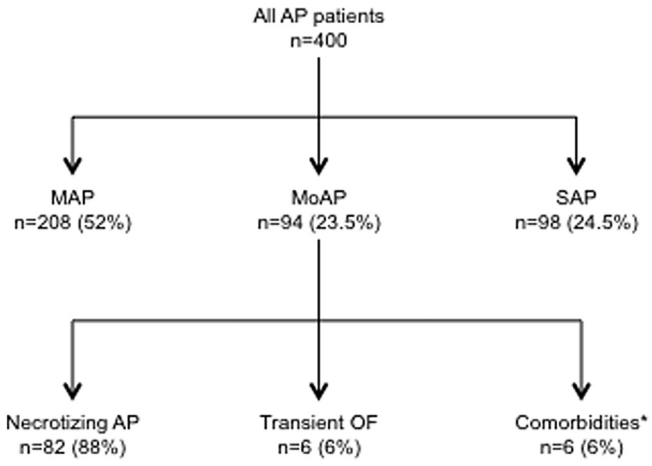

Fig. 1. Distribution of patients based on the Revised Atlanta severity Classification. *Exacerbation of underlying comorbidities. AP: acute pancreatitis; MAP: mild acute pancreatitis; MoAP: moderately severe acute pancreatitis; SAP: severe acute pancreatitis; OF: organ failure.

presentation and 70/91 (77%) at 48 h in the SAP grade. As seen in Table 1, patients with SAP had significantly higher median serum BUN levels than those with less severe disease, reaching 21 mg/dL (13, 35) on admission and 36 mg/dL (20, 52) at 48 h.

3.3. Pancreatic necrosis and infections

In our total cohort, 155 patients (39%) developed necrotizing AP. Parenchymal necrosis was identified in 124 (31%) and peripancreatic necrosis was seen in 31 (8%) patients. Out of 155 patients with necrotizing AP, infected necrosis was diagnosed in 30 (19%). Infected necrosis was more commonly identified in the SAP grade (23 out of 73; 32%) compared to MoAP (7 out of 82; 9%; $p < 0.001$; Table 3).

Extrapancreatic infections developed in 48 patients (12%). The most common site was the lungs (19 patients, 40%), while bacteremia was the second most common infection outside of the pancreas, diagnosed in 17 patients (35%). Extrapancreatic infection involved multiple sites for 17 (35%) patients. Infections were seen more commonly in tandem with increasing AP severity (Table 3). Out of 208 MAP patients, only 5 (2%) developed an extrapancreatic infection. The rate increased to 11/94 (12%) in the MoAP, and was the highest at 32/98 (33%) in the SAP grade ($p < 0.001$).

3.4. Management

Overall, the mean amount of IVF administered in the first 24 h was 4 L (±1.4). The amount of IVF that was given increased significantly from patients with MAP (3.7 ± 1.2) to those with MoAP (4.7 ± 1.6) and SAP (4.8 ± 1.9) ($p < 0.001$; Table 2).

ICU care was required in 125 of the 400 AP patients (31%), for a median of 10 days (3, 22). The majority of patients admitted to the ICU were from the SAP grade (n = 91; 73%), followed by MoAP (n = 22; 18%) and MAP (n = 12; 9%; $p < 0.001$). The 12 MAP patients who required ICU admission were predicted to have SAP upon presentation (n = 6), developed altered mental status from narcotic overdose (n = 3), had symptoms of alcohol withdrawal (n = 2), or had diabetic ketoacidosis (n = 1). In contrast, 7 SAP patients with single organ failure involving only the kidneys were managed on the regular hospital ward without requiring ICU care. The median duration of ICU care increased with disease severity from 3 days in the MAP to 4 in the MoAP and 14 in the SAP grade ($p < 0.001$; Table 2).

Nutritional support was provided to 150 AP patients (38%) and was initiated at an average of 5 days (3–7) from admission. The route of nutritional support was enteral in 98 patients, and TPN in 22 patients; 30 patients received both enteral and TPN. The need for nutritional support increased significantly with disease severity (Table 2). A small number of MAP patients developed smoldering symptoms, were unable to tolerate oral intake, and eventually received nutritional support (n = 14; 7%). Forty-eight out of 94 subjects with MoAP (51%) required nutritional support. Nutritional support was provided to the majority of SAP patients (n = 88; 90%; $p < 0.001$). The remaining 10 SAP patients either passed away early in the disease course before nutrition was initiated (n = 6), or

Table 2
Management of 400 Acute Pancreatitis patients stratified by the Revised Atlanta Classification.

	All AP n = 400	MAP n = 208 (52%)	MoAP n = 94 (23.5%)	SAP n = 98 (24.5%)	p-value
IVF the first 24 h, mean ± SD (liters)[a]	4 ± 1.4	3.7 ± 1.2	4.7 ± 1.6	4.8 ± 1.9	<0.001
ICU admission (%)	125 (31)	12 (6)	22 (23)	91 (93)	<0.001
ICU LOS, median days (IQR)	10 (3, 22)	3 (1, 4)	4 (2, 6)	14 (6, 28)	<0.001
Nutritional Support (%)	150 (38)	14 (7)	48 (51)	88 (90)	<0.001
▪ Enteral nutrition (%)	98 (25)	5 (2)	30 (32)	63 (64)	<0.001
▪ TPN (%)	22 (6)	5 (2)	12 (13)	5 (5)	0.001
▪ Both (%)	30 (8)	4 (2)	6 (6)	20 (20)	<0.001
Prophylactic antibiotics (%)	64 (16)	0	22 (23)	42 (43)	0.006
Drainage/debridement (%)	68 (17)	0	22 (23)	46 (47)	<0.001
Time of intervention, median days (IQR)	45 (21,73)	N/A	55 (29, 88)	30 (19, 70)	0.07

AP: acute pancreatitis; MAP: mild acute pancreatitis; MoAP: moderately severe acute pancreatitis; SAP: severe acute pancreatitis; IVF: intravenous fluids; ICU: intensive care unit; LOS: length of stay: TPN: total parenteral nutrition; IQR: interquartile range.
p-values represent trend test comparisons between MAP, MoAP, and SAP grades.
[a] Only data from patients directly admitted to our facilities were included.

Table 3
Outcomes of 400 Acute Pancreatitis patients stratified by the Revised Atlanta Classification.

	All AP n = 400	MAP n = 208 (52%)	MoAP n = 94 (23.5%)	SAP n = 98 (24.5%)	p-value
Necrotizing AP (%)	155 (39)	0	82 (87)	73 (74)	<0.001
Infected necrosis (%)	30/155 (19)	N/A	7/82 (9)	23/73 (32)	<0.001
Extrapancreatic infections (%)	48 (12)	5 (2)	11 (12)	32 (33)	<0.001
Hospital LOS, median days (IQR)	7 (5, 17)	5 (4, 7)	12 (7, 18)	29 (19, 43)	<0.001
Mortality (%)	21 (5)	0	0	21 (21)	N/A

AP: acute pancreatitis; MAP: mild acute pancreatitis; MoAP: moderately severe acute pancreatitis; SAP: severe acute pancreatitis; ICU: intensive care unit; LOS: length of stay.
p-values represent trend test comparisons between MAP, MoAP, and SAP grades.

developed single organ failure involving only the kidneys (n = 4) and tolerated oral feedings.

3.5. Specific management of necrotizing acute pancreatitis

Prophylactic antibiotics were administered to 64 out of 155 patients diagnosed with necrotizing AP (41%). The median time of prophylactic antibiotic initiation was 5 days. A significantly greater percentage of SAP patients with necrotizing AP received prophylactic carbapenem (42/73; 58%) when compared to MoAP patients (22/82; 27%, p < 0.001). There was no difference in the median time until carbapenem was started between the two groups.

Interventions for drainage/debridement of necrotic collections were performed in 68 out of 155 patients with necrotizing AP (44%) with a median intervention time of 45 days (21, 73) from presentation. Of 82 MoAP patients with necrotizing AP, 22 (27%) underwent drainage/debridement, at a median of 55 days (29, 88). A higher proportion of SAP patients required an intervention (46 out of 73, 63%) when compared to MoAP patients (p < 0.001), at a median of 30 days (19, 70, p = 0.07; Fig. 2).

3.6. Additional therapeutic modalities

ERCP was performed in 80 out of 155 patients with biliary AP (52%), 47 of which (30%) were performed urgently within the first 48 h. When compared to MoAP and SAP, patients with mild biliary AP more frequently required ERCP at any time during hospitalization (51/82, 62%; p < 0.001), but urgent ERCP utilization did not differ between the 3 severity grades. Nine out of 29 patients with MoAP underwent an ERCP (31%); four procedures were performed within the first 48 h (14%). Forty-four SAP patients had biliary AP and 20 of them underwent ERCP during hospitalization (45%), with 11 (25%) within 48 h of admission.

Fifty-six of 155 patients with biliary AP (36%) underwent a cholecystectomy during hospitalization and an additional 24 patients (15%) had a cholecystectomy following hospital discharge that could be tracked in our electronic medical records at a median of 65 days (42, 98). Cholecystectomy rates were similar between the MAP (45/82; 55%), MoAP (16/29; 55%), and SAP (19/44, 43%) grades (p = 0.42).

Plasmapheresis was performed in 8 out of 28 (29%) patients with hypertriglyceridemia-induced AP at a median time of 2 days from initial presentation. These 8 patients all developed SAP; the mean triglyceride level prior to plasmapheresis was 5829 mg/dL (±3566). Slightly more than 2/3 of the SAP patients with hypertriglyceridemia-induced AP required plasmapheresis. All MoAP and MAP patients with hypertriglyceridemia-induced AP were managed conservatively. Hemodialysis during hospitalization was required in 23 out of 73 (32%) SAP patients who developed persistent renal insufficiency at a median time of 3 days (2, 5) from presentation.

3.7. Hospital length of stay and mortality

The median length of hospital stay in our cohort was 7 days (5, 17). Hospitalization significantly increased with higher grades of severity (5 days in MAP, 12 days in MoAP, and 29 days in the SAP grade, p < 0.001; Table 3). The overall mortality rate in our cohort was 5% (n = 21). All 21 deaths occurred in the SAP grade as a result of overwhelming multi-system organ failure. Five patients died within the first week of hospitalization. Among the 21 patients who died, 13 underwent CECT scan and necrotizing pancreatitis was identified in all 13. Nine of the 21 patients underwent open surgery. Infected necrosis was diagnosed in 4 patients. Among 46 patients who underwent open surgery, 9 died (20%) compared to no deaths among the 22 patients who underwent minimally invasive interventions.

Five AP patients in our cohort died within the first week of hospitalization. These patients had multiple risk factors for severe disease. They were older (mean age: 57.8 years) and all but one were obese with a BMI $\geq$30 kg/m^2. Four out of five were diabetics and current smokers. Three out of 5 had biliary AP, 1 alcoholic, and

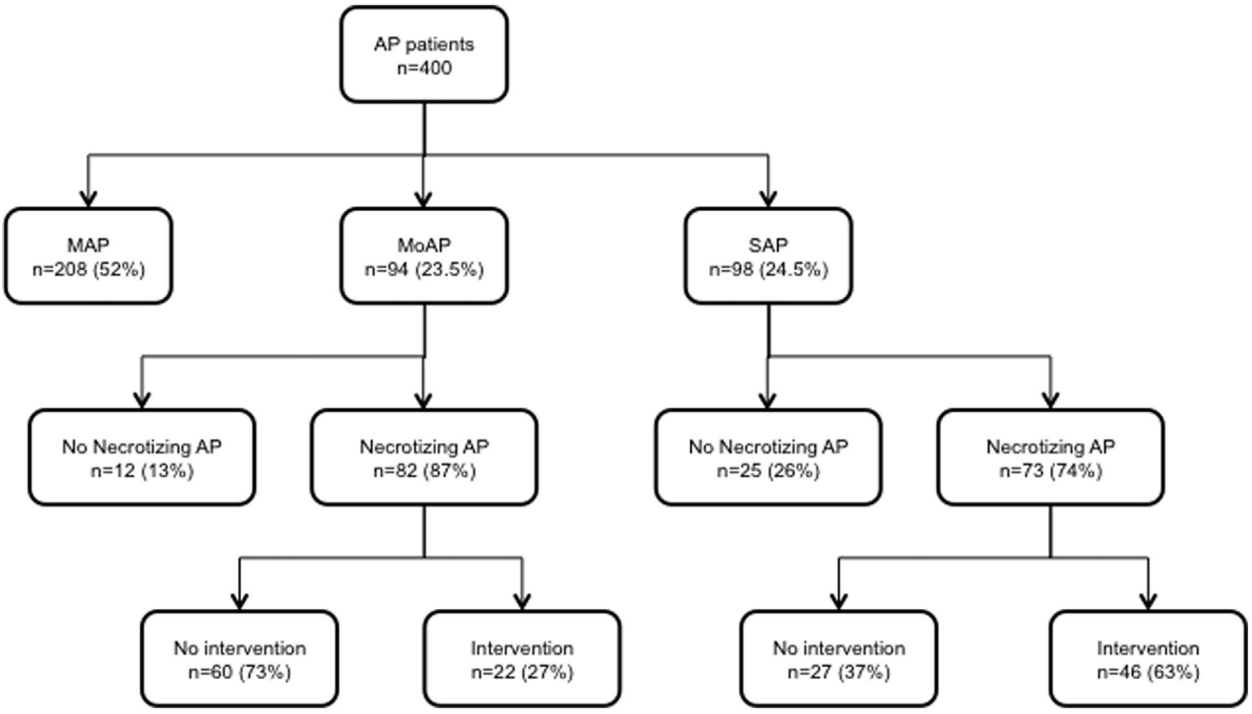

Fig. 2. Development of Necrotizing pancreatitis and Intervention (drainage/debridement) based on the Revised Atlanta Classification groups. Intervention in necrotizing AP of SAP (63%) vs. MoAP grade (27%), $p < 0.001$. AP: acute pancreatitis; MAP: mild acute pancreatitis; MoAP: moderately severe acute pancreatitis; SAP: severe acute pancreatitis.

1 hypertriglyceridemia-induced AP. All 5 patients were transferred to UPMC from an outside hospital. For 4 patients, this was their first episode of AP. All 5 patients died from multiple organ failure involving the cardiovascular, renal and pulmonary systems. One patient underwent an early open surgery for bowel ischemia, which was complicated by myocardial infarction and subsequent cardiac arrest. Statistical comparison with the rest of SAP patients was not performed, because of the very small number of patients in this group.

3.8. Clinical practice trends over time

In a post-hoc analysis, we compared the management of the first 191 AP patients enrolled between 2004 and 2008 versus the latter 209 who joined the study between 2009 and 2014. Persistent organ failure (SAP) developed in 42 (22%) and 56 patients (27%) and necrotizing AP in 69 (36%) and 86 patients (41%) during the first and second enrollment periods, respectively. There was a greater percentage of transferred patients in the later years (46% vs. 62%; $p = 0.001$).

The amount of IVF administration in the first 24 h did not change over the decade that encompassed our study (3.9 ± 1.37 vs. 4 ± 1.54 L). In the SAP grade, a greater quantity of fluid was given in the late phase, but this difference was not statistically significant (3.9 ± 1.6 vs. 5.2 ± 2 L; $p = 0.14$). In regards to the type of the IVF, Lactated Ringers solution begun to be used in the second phase of the study, but was still infrequently administered in the first 24 h (only in 18 patients). Fewer patients received ICU care in the first enrollment phase compared to the second phase [46/190 (24%) vs. 79/210 (38%); $p = 0.005$].

Nutritional support did not differ significantly between patients from the first (65/191; 34%) and second enrollment phases (85/209; 41%; $p = 0.18$). However, the use of enteral nutrition was more common (35/65 vs. 63/85; $p = 0.02$), while TPN was less likely to be used in AP patients over the decade (30/65 vs. 22/85, $p = 0.02$; Fig. 3).

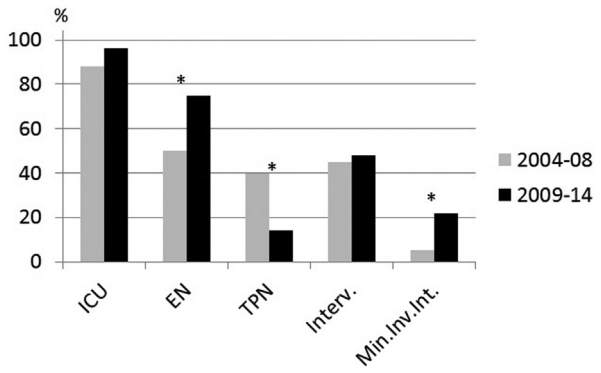

Fig. 3. Differences in management of patients with Severe Acute Pancreatitis in the early and late phase of the study. *$p < 0.05$. ICU: intensive care unit; EN: enteral nutrition; TPN: total parenteral nutrition; Interv.:intervention; Min.Inv.Int.: minimally invasive intervention.

In regards to the type of intervention, patients had a greater likelihood of undergoing minimally invasive procedures (laparoscopic surgery, endoscopic or percutaneous drainage) in the second phase of enrollment (17/41, 41%) in comparison to the first phase (5/27, 19%; $p = 0.048$; Table 4).

AP patients exclusively underwent plasmapheresis during the second enrollment phase of the study. More specifically, during the first phase, 7 patients were diagnosed with hypertriglyceridemia-induced AP, 3 of whom developed severe disease; none of these patients underwent plasmapheresis. In contrast, between 2009 and 2014, among 21 hypertriglyceridemia-induced AP patients, almost all of those with a severe disease course (8/9) underwent plasmapheresis. In the first period of the study, hypertriglyceridemia was managed conservatively. All SAP patients received prophylactic anticoagulation. Comparison of outcomes between patients with SAP who received plasmapheresis vs. those who did not was not

Table 4
Clinical characteristics, management and outcomes of acute pancreatitis patients between early and late phase in our center.

	All AP n = 400	2004–08 n = 191	2009–14 n = 209	p-value
Transfers (%)	217 (54)	87 (46)	130 (62)	0.001
SIRS at 48 h (%)	132/356 (37)	63/164 (33)	69/192 (33)	0.35
Persistent Organ Failure (%)	98 (25)	42 (22)	56 (27)	0.3
Necrotizing AP (%)	155 (39)	69 (36)	86 (41)	0.3
Hospital LOS, median days (IQR)	7 (5,17)	7 (4,15)	8 (5,18)	0.19
Mortality (%)	21 (5)	7 (4)	14 (7)	0.18
IVF the first 24 h, mean ± SD (liters)[a]	4 ± 1.4	3.9 ± 1.4	4.1 ± 1.5	0.41
▪ Lactated Ringers (%)[a]	19/192 (10)	1/103 (1)	18/89 (20)	<0.001
ICU admission (%)	125 (31)	46 (24)	79 (38)	0.003
ICU LOS, median days (IQR)	10 (3, 22)	8 (4, 21)	11 (3, 25)	0.46
Nutritional Support (%):	150 (38)	65 (34)	85 (41)	0.18
▪ Enteral nutrition (%)	98 (25)	35 (18)	63 (30)	0.006
▪ TPN (%)	22 (6)	12 (6)	10 (5)	0.51
▪ Both (%)	30 (8)	18 (9)	12 (6)	0.16
Prophylactic antibiotics (%)	64 (16)	26 (14)	38 (18)	0.2
Interventions (%)	68 (17)	27 (14)	41 (20)	0.34
▪ Minimally invasive (%)	22/68 (32)	5/27 (19)	17/41 (41)	0.048
▪ Time to intervention, median days (IQR)	44 (21, 73)	43 (17, 88)	45 (24, 66)	0.7

AP: acute pancreatitis; SIRS: systemic inflammatory response syndrome; IVF: intravenous fluids; ICU: intensive care unit; LOS: length of stay: TPN: total parenteral nutrition; IQR: interquartile range.
[a] Only data from patients directly admitted to our facilities were included.

performed because of the small number of patients in both groups.

No significant differences were observed in respect to the frequency of ERCP [37/64 (58%) vs. 43/91 (47%)], and hemodialysis [6/27 (22%) vs. 17/49 (35%), both p > 0.20] between the two phases of enrollment.

4. Discussion

To our knowledge, this is the largest study in the U.S. to report details in management and clinical outcomes of AP patients stratified by RAC. We also describe trends and changes in AP management over the course of the last decade in our institution.

Between the two updated Severity Classification systems, we elected to utilize the RAC [5], because it focuses more on the early, dynamic nature of AP, and is clinically relevant to daily practice [8]. Our group had previously directly compared RAC and DBC and found that RAC was easily applicable and classified about half of patients as having mild disease, while about a fourth of them were categorized as having moderately severe or distinctly severe disease course. Compared to our prior report, the present study focuses on the management practices of AP over the last decade. Detailed report of large tertiary centers' experiences on AP management may increase clinicians' awareness and guide their practice. The high prevalence of SAP and necrotizing pancreatitis in our cohort, when compared to a recent study from a community hospital in Europe [17], likely reflects our institution's role as a well-known, local referral center.

The RAC defines MoAP as a heterogeneous group of patients based on 3 independent criteria. We found that two of the three criteria for MoAP, local complications and transient organ failure, were easily recognizable. However, the third criterion, exacerbation of underlying comorbidities, was much more difficult to discern. The RAC definition does not clarify which comorbidities should be included and how to define “exacerbation”. In our cohort, we only identified 6 patients having MoAP based on the exacerbation of comorbid conditions. Furthermore, other small subgroups of patients appeared to demonstrate a similar clinical course. For example, MAP patients who developed smoldering symptoms requiring nutritional support and those with extrapancreatic infections both had prolonged hospitalization. Based on the above limitations, we propose the RAC working group to consider clarifying or even removing “exacerbation of underlying comorbidities” as a criterion of MoAP. Finally, MoAP appears to be a diverse group in terms of disease clinical course, ranging from minimal peripancreatic necrosis or mild, transient increase in creatinine to infected pancreatic necrosis requiring intervention [18]. Further discussion among experts and a general consensus is needed for improved definitions of acute pancreatitis patients with intermediate severity.

In this study, we report in detail myriad aspects of conservative and interventional management practiced in our center during the last decade. Many of our findings may be of interest to clinicians who are involved in the care of pancreatitis patients. We elected to reference management to time of initial presentation of patients to a health care facility and not to time of symptoms onset, so as to reflect the time point when physicians may impact the clinical course of pancreatitis. In respect to fluid resuscitation, there are only a few studies investigating the role of IVF, which are limited by small size [19] or shortcomings in their study design [20–22]. In our cohort, the mean amount of IVF administered within the first 24 h reached 4 L and was significantly higher in patients with MoAP and SAP when compared to MAP. The average amount of IVF administered did not appear to change over time.

Nutritional support plays an important role in AP patients with organ failure who are unable to eat. It is also used to achieve pancreatic rest in patients with extensive necrotizing pancreatitis. In respect to the timing of nutritional support, a recent randomized controlled trial of AP patients at high risk for complications did not show any benefit of early enteral (within 24 h) versus oral feedings on demand (at 72 h after presentation) in terms of infections and mortality [23]. In our study, nutritional support was initiated in approximately 1/3 of all AP patients, mainly in patients with MoAP and SAP, at a median of hospital day 5. Clinicians should recognize that a minority of MAP patients might fail oral challenge and eventually require nutritional support. Of importance, utilization of enteral nutrition has been increasing in contrast to TPN use in our practice through the years.

More than one third of the patients (39%) in this cohort developed necrotizing pancreatitis. Infected necrosis was diagnosed in almost one fifth (19%) of them, which is a rate relatively lower than

what has been noted in recent literature (16%–47%) [24]. The smaller percentage of infected necrosis in our cohort may reflect a true decrease in its prevalence due to prescribing prophylactic antibiotics and utilizing enteral nutrition, as well as a reduction in the use of invasive diagnostic methods, such as fine needle aspiration.

The role of prophylactic antibiotics in necrotizing pancreatitis remains controversial. Several heterogeneous studies have produced disparate results in regards to infection. In a Cochrane meta-analysis, the effects of prophylactic antibiotics did not reach statistical significance overall, while the administration of imipenem resulted in significant reduction of pancreatic infection in post-hoc analysis [25]. Furthermore, a recent meta-analysis reported benefit in prophylactic use of antibiotics in patients with extensive PNec [26]. In our study, approximately 40% of patients with necrotizing pancreatitis received prophylactic meropenem, which may simply reflect physician choice based on experience given the conflicting literature. The frequency of antibiotic use in our institution did not change over time.

In respect to treatment of local complications, fewer than 50% of patients with necrotizing pancreatitis underwent drainage/debridement of necrotic collections in our center, which is similar to a recent report from a large European cohort [27]. Delayed intervention for extensive walled-off pancreatic necrosis was required for symptomatic patients. This group included patients with abdominal pain, symptoms of gastric outlet obstruction, biliary obstruction, failure to thrive, and also those with signs of infection. In our experience, not all patients with symptomatic pancreatic necrosis develop infected necrosis. Patients with pancreatic necrosis who do not develop persistent organ failure are considered as moderately severe by the RAC. In terms of the types of interventions that were performed, minimally invasive procedures such as laparoscopic necrosectomy, percutaneous drain placement, or endoscopic drainage/debridement have been utilized more frequently over time. These findings are in line with a recent randomized controlled trial showing that a step-up minimally invasive approach results in fewer complications and better outcomes when compared to open surgery [27–29]. Finally, the median time from presentation to the first intervention in symptomatic necrotizing pancreatitis patients was 45 days, which is in accordance with recent studies and committee guidelines recommending to delay interventions as long as possible [27].

In respect to specific treatments based on the etiology of AP, in our center, plasmapheresis within the first 48 h of admission is emerging as first-line therapeutic approach in patients suspected of having severe hypertriglyceridemia-induced AP. However, well-designed, randomized controlled studies to support this therapy are lacking.

Despite the statistically significant change in certain aspects of AP management over time in our institution, only 20% received Lactated Ringers, 41% underwent minimally invasive procedures for pancreatic drainage/debridement and still 18% received prophylactic antibiotics in the second phase of the study between 2009 and 2014. Even though the above trends have continued to improve over the last year, it appears that certain aspects of AP management in our institution lag behind the evidence. Further work is needed to identify areas where improvements can be achieved, as well as tools for assisting clinical implementation of novel therapeutic approaches in a timely fashion.

In addition, the statistically significant changes in certain aspects of the management of AP between the two phases of the study did not result in better outcomes. This finding is likely multifactorial: the increased percentage of transferred patients in our facility, increased ratio of patients with certain risk factors, e.g. triglyceridemia-induced AP and obesity over time could potentially explain the above. Furthermore, there could be an improvement in other outcomes related with the quality of life, such as duration of abdominal pain, extent of pancreatic damage, and late outcomes. However, the above outcomes were not assessed in this study.

Mortality was only seen in the SAP grade and reached 21% in our study. This rate appears to be lower than other recent reports of an approximate death rate of 30% for individuals with a severe disease course [30]. The lower mortality in the present study could reflect advanced management practices. It may also represent a selection bias, because a portion of patients with fulminant, multisystem organ failure die within days, prior to being transferred to a tertiary center. The 21 patients that died in our cohort suffered multi-organ failure that began within days of presentation. Furthermore, of those who underwent imaging, all had evidence of necrosis on CECT scan; this finding supports that the coexistence of persistent organ failure with necrosis, especially infected necrosis, drives mortality as suggested by Petrov et al. [30] All patients who died within days from their hospitalization had multiple risk factors for severe disease including older age, obesity, concomitant diabetes melitus, and current smoking.

Our study has several strengths. To our knowledge, this study is the first to provide an extensive report on numerous aspects of management as well as clinically-relevant outcomes of AP patients stratified into severity grades according to the RAC. The prospective and consistent nature of patient enrollment in our study eliminates selection bias. Furthermore, we have a sizeable number of well phenotyped patients. Finally, our study enrollment spanned a decade, allowing us to compare clinical practice patterns and follow changes that evolved in AP patient management.

This study has several potential limitations. Firstly, as previously mentioned, our institution is a referral center that treats a large number of very ill patients who require more advanced types of therapy. This is reflected in the high prevalence of MoAP and SAP grades in our cohort. Second, being a tertiary center highly experienced in managing complicated cases, some of our therapeutic approaches may not be applicable to AP patients who are seen at smaller, community hospitals. Third, there were recent revisions to the classification of AP severity and local complications in the RAC. In the earlier study phase, treating clinicians would have been unaware of the newly established RAC grades, which may have biased some of our findings. Finally, CECT scans were performed based on the discretion of treating physicians. A small number of local complications could have been overlooked in patients who did not undergo CECT scans.

In conclusion, we found that management and clinical outcomes of AP patients differed significantly between the three RAC severity grades. Under the care of our participating physicians, over half of patients with necrotizing AP are managed conservatively. Changes that we noted over time include preferential use of enteral nutrition rather than TPN, increase in the number of minimally invasive procedures compared to laparotomy and the use of plasmapheresis to treat AP caused by hypertriglyceridemia. Interestingly, despite being a referral center, the mortality rate in our cohort was low in comparison to historical data, likely reflecting therapeutic advancements in managing patients with a severe disease course. The present is the largest to date empiric study reporting details on management and clinical outcomes of AP patients categorized by RAC.

Disclosures

None of the authors have any potential conflicts (financial, professional, or personal) that are relevant to the manuscript.

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