Pediatric Acute Pancreatitis

Changes in Management and Disease Outcomes Over 16 Years

Liron Birimberg-Schwartz, MD, Sara Rajiwate,* Annie Dupuis, PhD,† and Tanja Gonska, MD*‡*

Objective: To examine the changes over time of pediatric acute pancreatitis (AP) severity, management, and disease outcomes at our academic tertiary center.

Methods: We reviewed 223 pediatric AP admissions (2002–2018) and used a time-to-event regression model to study changes over time. Disease outcomes were analyzed using a subgroup of 89 patients in whom only the AP event determined length of hospital stay and duration of opioid use.

Results: There was an increase in mild, but not severe, AP episodes over the examined period. June 2014 was identified as a single cutoff point for change in AP management and disease outcomes independent of each other and of disease severity. Timing of initiating enteral nutrition decreased from 5 to 1.6 days ($P < 0.0001$) in the entire cohort and from 4.1 to 1.8 days in the subgroup ($P = 0.0001$) after June 2014. Length of hospitalization decreased from 6 to 3.3 days ($P = 0.0008$) and days of opioid use from 4.1 to 1.3 ($P = 0.002$) after June 2014.

Conclusions: Timing of initiating enteral nutrition has significantly reduced at our center after June 2014. In parallel, we observed a significant improvement in disease outcomes.

Key Words: pediatric acute pancreatitis, disease severity, early enteral nutrition, fluid management, disease outcomes

Abbreviations: AP - acute pancreatitis, IV - intravenous, LOS - length of hospital stay

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Acute pancreatitis (AP) is an acute, typically self-resolving inflammation of the pancreas.[1,2] The incidence of AP in children is in the range of 3 to 13 cases per 100,000 persons per year.[2–6] In most pediatric cases, AP resolves and patients have no further complications related to pancreatitis. However, a subset of children (15–20%) develops complications ranging from local pancreatic complications to the development of systemic inflammatory responses, which may result in a more severe disease course and prolonged hospitalization.[7–9]

Adequate intravenous (IV) fluid and nutritional management are critical aspects when managing AP episodes. In the past 2 decades, several randomized controlled trials and meta-analyses in adults demonstrated that early enteral nutrition decreased length of hospital stay (LOS) and reduced infectious complications and mortality.[10–17] These data led to a dramatic change in the nutritional management of AP in adults from initially complete bowel rest to early oral feeding and enteral nutrition even in patients with predicted severe pancreatitis.[18,19] Recent studies in adults have shown that fluid resuscitation not only maintains adequate fluid status in AP but also reduces the risk of complications, such as necrosis and organ failure.[20,21]

Data on the benefit of early enteral nutrition and the optimal fluid administration rate in pediatric AP are limited.[22–24] Nevertheless, the significant benefits demonstrated in adult AP studies led to the adaption of early enteral feeding and aggressive fluid management in the recently published guidelines for management of pediatric AP.[25,26]

In this retrospective study, we used the recently established pediatric AP classification guidelines to examine changes in pediatric AP severity over the past 16 years at our center. We then reviewed our center's experience with respect to pediatric AP nutritional and fluid management practices, and whether this management has changed over time. Finally, we evaluated changes in disease outcomes, specifically LOS and length of opioid requirement.

MATERIALS AND METHODS

Study Design and Cohort

This was a single-center retrospective study conducted at the Hospital for Sick Children in Toronto, Canada. The study was approved by the hospital's research ethics board (REB #1000060079). Medical charts of 348 children who were admitted with a diagnosis of AP between January 2002 and July 2018 were reviewed. Of those, we included 223 patients who met the diagnostic criteria for AP[27] and for whom sufficient clinical data were available for our analysis (Fig. 1). We only included data regarding the first AP episode for patients with recurring AP episodes. Additionally, we defined a subgroup of patients for whom the AP episode was the only indication for hospitalization without any additional diagnosis or medical circumstances that may have affected LOS or pain management (Fig. 1).

Definitions

Acute pancreatitis was diagnosed if patients met at least 2 of the following diagnostic criteria: (1) clinical symptoms consistent with AP (primarily abdominal pain as well as nausea and/or vomiting), (2) elevated serum lipase or amylase 3 times or higher the upper limit of the normal reference range, and/or (3) imaging evidence of pancreatitis.[27] Episodes were classified as mild AP in the absence of organ failure or local/systemic complications and as moderately severe if the patient developed transient organ failure/dysfunction or developed local or systemic complications. Acute pancreatitis was classified as severe if the patient developed organ dysfunction/failure that persisted longer than 48 hours.[28] Cardiovascular, respiratory, and renal dysfunction were defined according to the International Pediatric Sepsis Consensus,[29] as recommended in the pediatric AP classification algorithm.[28]

Enteral nutrition was considered as any form of food taken into the gastrointestinal tract–by mouth, gastric, duodenal, or jejunal route. Early enteral nutrition was defined as enteral feeding within 48 hours of presentation. Aggressive fluid management

From the *Department of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children; †Department of Biostatistics, and ‡Department of Pediatrics, University of Toronto, Toronto, Canada.

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Address correspondence to: Liron Birimberg-Schwartz, MD, Department of Pediatrics, Hadassah Medical Center, 1 Kalman Mann St, Jerusalem, Israel (e-mail: lbschwartz@hadassah.org.il).

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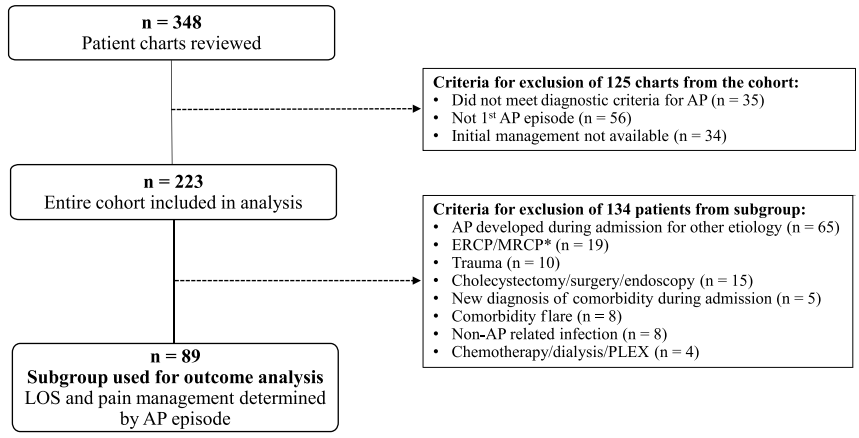

FIGURE 1. Study patient flow. *Patients with MRCP were excluded because of limited availability of the MRI scanner that may have affected LOS. ERCP, endoscopic retrograde cholangiopancreatography; PLEX, plasma exchange; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging.

was defined as at least 1.5× maintenance fluids given at the time of admission.

Data Collection and Outcomes

Data collected included the patient's age, sex, weight, underlying comorbidities, the etiology of the AP episode, details of clinical presentation, fluid and nutritional management, the development of organ failure, complications that developed during the admission and interventions during the admission. Furthermore, we collected data on the LOS, duration of analgesia, and the need for opioids for pain management.

Statistical Methods

Data are presented as mean (standard deviation [SD]) or median (interquartile range [IQR]), as appropriate for their normality of distribution. χ^2 test was used for categorical variables, analysis of variance was used for continuous variables, and odds ratios were used for binary variables when comparing groups. A linear regression model was applied to study the effect of the year of admission on disease severity. A P value less than 0.05 was set as the significance threshold. Given the small number of severe AP episodes, we combined moderately severe with severe AP episodes when performing comparative analyses with mild AP.

A time-to-event regression model assuming a log normal distribution of event times was used to evaluate changes in the day of initiation of enteral feeds, day of discharge, and the day of discontinuing opioids. To determine if the change in outcomes took place gradually across time or more suddenly at a single cutoff point, we compared the likelihood ratio of the model treating date as a continuous variable to a model that categorized the data into 2 periods, with the cutoff point selected to maximize the likelihood of the model. We further tested a period × continuous date interaction to look for gradual changes over and above the period effect across the 2 periods identified in the cutoff point analysis.

RESULTS

Cohort Description

A total of 223 patients who met the diagnostic criteria for AP and for whom sufficient clinical data were available were included in the analysis (Fig. 1). Table 1 summarizes the demographic and baseline characteristics of the study cohort. At the time of the AP episode, 125 (56.1%) of 223 patients had a comorbidity with inflammatory bowel disease and leukemia/lymphoma being the most common (Table 1). The etiology of the AP episode was identified in 140 (62.8%) of 223 patients with medication-induced AP (23.3%) and biliary disease (17.9%) being the most common causes (Table 1).

Disease Severity

When we applied the recently published classification criteria,[28] we classified 187 (83.9%) episodes as mild AP, 26 (11.7%) episodes as moderately severe AP and 10 (4.5%) episodes as severe AP (Table 2). The complications and types of organ failure that developed during the AP episode are specified in Table 2. Disease severity was determined at the time of admission or within 48 hours in 28 (78%) of 36 moderate-severe/severe AP patients. We observed an increase over time in the number of mild AP episodes diagnosed per year at our center, whereas the number of moderately severe/severe AP episodes remained stable (Fig. 2).

We did not identify any difference in disease severity according to sex ($P = 0.69$), age ($P = 0.66$), or weight ($P = 0.34$). When evaluating for a possible association between concomitant comorbidity and AP severity in the groups of patients with a sufficient sample size, we observed that patients with an underlying diagnosis of leukemia/lymphoma or a neurological disorder had a higher risk of having moderately severe/severe AP with odds ratios of 3.04 (95% confidence interval [CI], 1.2–7.73; $P = 0.02$) and 4.32 (95% CI, 1.21–15.41; $P = 0.02$), respectively, compared with patients without a comorbidity.

Time-to-Event Model Identified a Single Timepoint of Change

We used a time-to-event regression model to assess changes in nutritional management and disease outcomes over time. Because the likelihood for the model that divided the data into 2 periods was greater than the likelihood for the model treating the date as a continuous variable, we chose to compare variables between 2 periods. Remarkably, June 2014 was independently found to be a significant cutoff point when analyzing both changes in timing of feeds and LOS over time. There was no gradual change over time within each period when looking at timing of feeds, LOS and duration of opioid use, rather a sudden change observed at the timepoint of June 2014. We subsequently used the cutoff

TABLE 1. Demographics and Baseline Characteristics of the Entire AP Cohort and Subgroup*

	Entire Cohort (n = 223)	Subgroup (n = 89)
Age, mean (SD), y	11 (4.8)	10.7 (4.7)
Sex, male, n (%)	111 (49.8)	40 (44.9)
Weight, *z* score, median (IQR)	0.26 (−0.66 to 1.29)	0.52 (−0.39 to 1.59)
Co-morbidity, n (%)		
Leukemia/lymphoma	36 (16.1)	7 (7.9)
Inflammatory bowel disease	30 (13.5)	9 (10.1)
Neurological disorder†	13 (5.8)	7 (7.9)
Diabetes	8 (3.6)	1 (1.1)
Hemolytic anemia	7 (3.1)	2 (2.2)
Renal disease‡	7 (3.1)	2 (2.2)
Liver disease§	6 (2.7)	3 (3.4)
Genetic disorder	4 (1.8)	2 (2.2)
Metabolic disorder	4 (1.8)	1 (1.1)
Cystic fibrosis	3 (1.3)	2 (2.2)
Other‖	7 (3.1)	1 (1.1)
Total number patients with a co-morbidity	125 (56.1)	37 (41.6)
Etiology of AP episode, n (%)		
Medication-induced	52 (23.3)	16 (18)
Biliary disease	40 (17.9)	12 (13.5)
Trauma	11 (4.9)	–
Anatomical	8 (3.6)	5 (5.6)
Postendoscopic retrograde cholangiopancreatography	8 (3.6)	–
Metabolic	7 (3.1)	2 (2.2)
Inflammatory bowel disease	4 (1.8)	–
Hereditary	4 (1.8)	3 (3.4)
Infectious	3 (1.3)	1 (1.1)
Autoimmune	3 (1.3)	1 (1.1)
Total number patients with known etiology	140 (62.8)	40 (44.9)

Frequencies (%), mean (SD), or median with (IQR) are presented as appropriate.

*Subgroup = patients included in outcome analysis for whom LOS stay and pain management were determined only by the AP episode.

†Seizures, cerebral palsy, megalencephaly.

‡Nephrocalcinosis, nephrotic syndrome, chronic renal failure.

§Caroli disease, intestinal failure associated liver disease, liver transplant recipient, chronic liver disease.

‖Hemophagocytic lymphohistiocytosis, myelodysplastic syndrome, systemic lupus erythematosus, Langerhans cell histiocytosis, dilated cardiomyopathy, Wegener granulomatosis, asthma.

point of June 2014 established from this model, to assess significant changes of the other variables.

Enteral Nutritional and Fluid Management

There was a significant change in the time from hospital admission to initiating enteral nutrition decreasing from 5 days (95% CI, 4.3–5.8) before June 2014 to 1.6 days (95% CI, 1.2–2) after June 2014 ($P < 0.0001$) (Table 3). Furthermore, when comparing the 2 study periods established from the time-to-event model, we found an increase in the proportion of patients who received early enteral nutrition after June 2014 compared with before June 2014 (69% vs 25.4%, $P < 0.0001$) (Table 3). A similar significant decrease in the time from hospital admission to initiating enteral nutrition was also seen in the subgroup (Fig. 3 and Table 3) and when focusing on only the mild AP episodes (Table 3). Generally, enteral nutrition was initiated earlier in patients with mild AP compared with those with moderately severe/severe AP episodes; 3 days (IQR, 1–3 days) versus 9 days (IQR, 5–15 days), respectively ($P < 0.0001$).

A total of 186 (84.2%) of the 221 patients for whom fluid management data were available, were given IV fluids upon presentation with AP; however only 37 (19.9%) of 186 received an IV fluid rate of 1.5× maintenance or greater. There was no significant change in fluid management over time (Table 3). Higher fluid volumes were more frequently administered to patients with more severe AP episodes: 11 (34.4%) of the 32 patients with moderately severe/severe AP compared with 26 (16.9%) of the 154 patients with mild AP, $P = 0.02$.

Disease Outcomes

We observed a significant change in LOS over time that decreased from 6 days (95% CI, 4.9–7.5) before June 2014 to 3.3 days (95% CI, 2.4–4.3) after June 2014, $P = 0.0008$ (Fig. 3). When evaluating only the mild AP cases to account for the disparity of moderately severe/severe AP cases between the 2 study periods in the subgroup (Table 3), we similarly found a significant reduction in LOS from 3.8 (95% CI, 3.2–4.6) days before June 2014 to 2.8 (95% CI, 2.2–3.4) after June 2014, $P = 0.026$ (Table 3).

TABLE 2. Descriptive Statistics in the Entire Cohort and the Subgroup*

	Entire Cohort (n = 223)	Subgroup (n = 89)
AP severity, n (%)		
Mild	187 (83.9)	70 (78.7)
Moderately severe	26 (11.7)	11 (12.4)
Severe	10 (4.5)	8 (9)
Complications, n (%)		
Pseudocyst	18 (8.1)	10 (11.2)
Necrotizing pancreatitis	9 (4)	7 (7.9)
Pancreatic fluid collection	8 (3.6)	2 (2.2)
Intensive Care Unit admission	5 (2.2)	3 (3.4)
Thrombotic event	3 (1.3)	3 (3.4)
Total number of patients with ≥1 complications	36 (16.1)	19 (21.3)
Organ failure, n (%)		
Respiratory	11 (4.9)	7 (7.9)
Cardiovascular	4 (1.8)	2 (2.2)
Renal	3 (1.3)	1 (1.1)
Total number patients with single/ multiple organ failure	13 (5.8)	10 (11.2)

*Subgroup = patients used for outcome analysis for whom LOS and pain management were determined only by the AP episode.

Opioid use was recorded in 46 (51.7%) of the 89 patients in the subgroup. Patients admitted after June 2014 received a significantly shorter duration of opioid therapy of 1.3 days (95% CI, 0.7–2.5 days) compared with 4.1 days (95% CI, 2.8–6.1 days) before June 2014 ($P = 0.002$) (Table 3). This observation was similar for the patients with mild AP within the subgroup, although this difference did not reach statistical significance (Table 3).

DISCUSSION

In this retrospective study, we demonstrated that the diagnosis of moderately severe/severe AP episodes remained stable over the last 16 years. Management of AP at our center has changed with regard to nutritional, but not fluid management, toward earlier initiation of enteral nutrition starting from June 2014. Although causality cannot be established, we observed a clinically pertinent reduction in LOS and duration of opioid use that occurred at the same timepoint as the nutritional management changes.

In this study, we are the first to apply the recently published consensus on the classification of pediatric AP[28] to report on how AP severity changed over time at our center. Our study was not designed to report on pediatric AP incidence, nevertheless, we were able to show that the number of moderately severe/severe AP episodes per year remained stable over time whereas the number of mild AP episodes increased. Next to a possible true increase in AP cases, the later could also be explained by an increased awareness of pediatric AP that led to more testing and hence improved detection of mild AP episodes that could have been missed in earlier years.[2,3,30–32]

The majority of the patients in our cohort with moderately severe/severe AP were classified as such within 48 hours of admission, which argues against the impact of clinical management decisions regarding the time of initiating enteral feeds on the severity of the AP episode. This observation, together with the finding that patients with moderately severe/severe AP were fed later than patients with mild AP, suggests that it was the AP severity that influenced management decisions, and not vice versa. It appears that physicians at our center were still hesitant to initiate early enteral nutrition in the more severe AP episodes. The explanation for this hesitation is most likely multifactorial, including potential fear to worsen the patient's clinical status, concern that the patient may require urgent intervention, or a persistent misconception on the benefit of bowel rest in AP.[2,33] This could be best overcome with a prospective randomized controlled study in children with moderately severe/severe AP, similar to what has been done in adults. However, the low frequency of moderately severe/severe AP in children challenges such an undertaking.[8,28,34]

At our center, children with AP received earlier enteral nutrition starting from June 2014. The timing of this change is notable because at that timepoint the pediatric guidelines were not yet published[25,26]; however, there were already substantial data from adult studies regarding the benefit of early enteral nutrition in AP management including updated adult AP guidelines.[12–19,35] At the same timepoint of June 2014, we also observed an improvement in disease outcomes, specifically shorter LOS and duration of opioid use. The improvements in disease outcomes we observed are

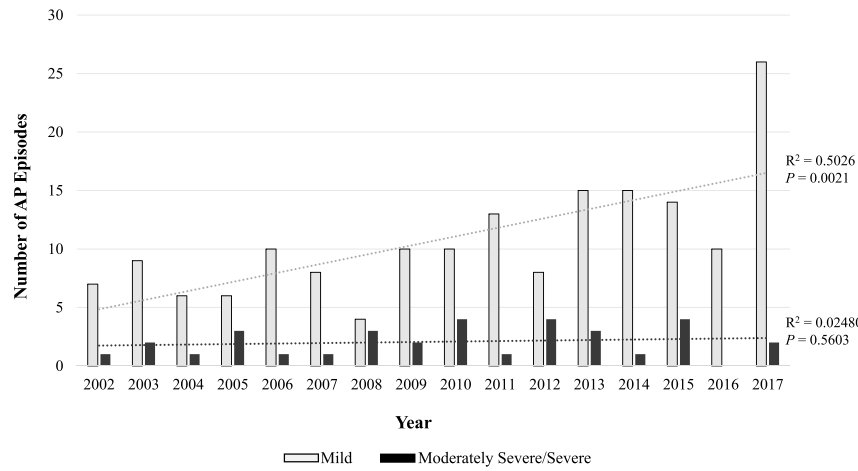

FIGURE 2. Changes in disease severity over the 16–year study period. Bars represent the number of mild and moderately severe/severe AP episodes per year. Linear regression analysis demonstrates a significant increase in mild AP episodes over time. The year 2018 was not included because only partial data until June 2018 were available.

TABLE 3. Summary of Results When Comparing the 2 Periods Using June 2014 as the Cutoff Point*

	January 2002–May 2014	June 2014–June 2018	χ^2	*P*
Entire cohort				
Early enteral feeds within 48 h (n = 214)	33/130 (25.4)	58/84 (69)	39.8	<0.0001
Aggressive IV fluid management – ≥1.5× maintenance (n = 186)	19/112 (17)	18/74 (24.3)	1.5	0.22
Day of initiating enteral feeds (n = 214)	5 (4.3–5.8)	1.6 (1.2–2)	73.3	<0.0001
Mild AP within the entire cohort				
Day of initiating enteral feeds (n = 179)	4 (3.4–4.7)	1.4 (1.1–1.8)	57.3	<0.0001
Subgroup†				
Proportion of moderately severe/severe AP to mild AP episodes	18/40 (45)	1/30 (3.3)	9.3	0.002
Day of initiating enteral feeds (n = 88)	4.1 (3.3–5.1)	1.8 (1.2–2.6)	14.9	0.0001
LOS (n = 89)	6 (4.9–7.5)	3.3 (2.4–4.3)	11.2	0.0008
Duration of opioid use (n = 46)	4.1 (2.8–6.1)	1.3 (0.7–2.5)	9.5	0.002
Mild AP within the subgroup				
Day of initiating enteral feeds (n = 70)	2.5 (2.0–3.1)	1.5 (1.1–2.0)	8.6	0.003
LOS (n = 70)	3.8 (3.2–4.6)	2.8 (2.2–3.4)	73.4	0.026
Duration of opioid use (n = 28)	1.9 (1.3–2.8)	1.1 (0.7–1.7)	3.4	0.07

*Results from the time-to-event model assuming a log normal distribution of event times are presented as median days (95% CI), all other results are presented as proportions (%).

†Subgroup = patients included for outcome analysis for whom LOS and pain management were determined only by the AP episode.

clinically meaningful and without a doubt have already affected patient satisfaction and disease management costs. Although the retrospective nature of our study does not allow drawing direct conclusions of causality between the changes in nutritional management and the improved disease outcomes, the fact that they occurred at the same timepoint at the very least suggests that early enteral nutrition did not adversely affect disease outcomes in our cohort and was safe to implement.

The majority of patients at our center did not receive aggressive IV fluid management, and this has not changed over time. In contrast to nutritional management, sufficient evidence regarding optimal fluid management in AP is lacking. The current adult AP guidelines suggest using goal-directed therapy for fluid management of AP, although the evidence basis for optimal fluid therapy in AP is weak.[19,36] In pediatric AP, a single study showed that a combination of early enteral nutrition (<48 hours) and aggressive fluids (>1.5–2× maintenance in the first 24 hours) decreased LOS and the occurrence of severe disease in comparison to more conventional historical management.[23] Nevertheless, the general lack of evidence regarding optimal fluid management in AP, together with concern of fluid overload in certain medical conditions, might explain why patients at our center are not receiving aggressive fluid management when presenting with AP. Future studies would be important to evaluate whether initial aggressive IV fluid management can improve the outcomes of moderately severe and severe pediatric AP.

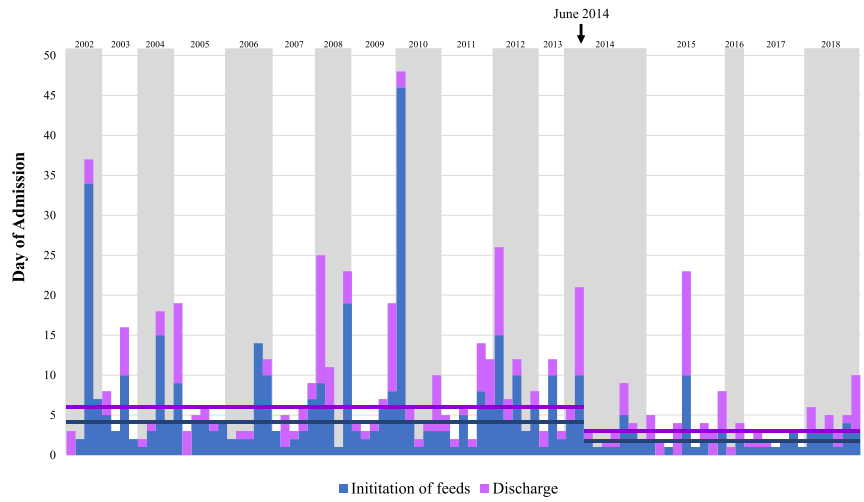

FIGURE 3. The number of days to initiation of feeds (blue bars) and the number of days to discharge (purple bar) are demonstrated for each patient of the subgroup (n = 89) grouped by the year of occurrence. The horizontal lines represent the median of days in each study period with confidence intervals demonstrating a significant decrease in the day of admission initiating feeds ($P = 0.0001$) and day of discharge ($P = 0.0008$) since June 2014. **Editor's note:** A color image accompanies the online version of this article.

The main limitation of our study is that the retrospective nature of our analysis does not allow us to determine direct causality between clinical management and disease outcomes. Further, adhering to stringent inclusion criteria limited our sample size, in return for increasing the accuracy and validity of our results. In addition, this study reflects a single-center experience and thus comprises a selection bias in terms of cases treated at our center and management approaches.

In summary, we observed a significant and clinical meaningful improvement in pediatric AP outcomes at our center. Furthermore, over recent years, our center has changed AP management toward earlier initiation of enteral nutrition. Although causality cannot be established, we believe our study demonstrates that early enteral nutrition is safe when managing pediatric AP.

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