CME

Acute Pancreatitis in the Pediatric Intensive Care Unit

*Praveen S. Goday, †Martin Wakeham, ‡Evelyn M. Kuhn, ‡Maureen M. Collins, and *Steven L. Werlin

ABSTRACT

Aim: The aim of this study is to describe the demographics and outcomes of children with a discharge diagnosis of acute pancreatitis (AP) from the pediatric intensive care unit (PICU).

Methods: Data for this retrospective cohort study were obtained from a multisite, clinical PICU database. PICU discharges with a primary or secondary diagnosis of AP (SAP) between 2009 and 2013 from 113 centers were reviewed. We also obtained the Pediatric Index of Mortality 2 Risk of Mortality (PIM2ROM), an indicator of the severity of illness.

Results: Of 360,162 PICU discharges, 2026 with a diagnosis of AP were analyzed further (0.56%)—331 had a primary diagnosis of AP, whereas 1695 had a SAP. Among children with primary AP, median PIM2ROM was 1.0% (interquartile range [IQR] 0.8%–1.4%). Fifty-five children with primary AP (16.6%) required mechanical ventilation (MV) for a median of 3.8 days (IQR 1.0–9.3). The length of stay (LOS) in PICU was a median of 2.95 days (IQR 1.53–5.90). Only 1 patient died (mortality 0.3%). Among children with secondary AP, median PIM2ROM was 1.1% (IQR 0.8%–4.0%). A total of 711 children (42.0%) with secondary AP required MV for a median of 5.8 days (IQR 1.8–14.0). PICU LOS was a median of 4.43 days (IQR 1.84–11.22). There were 115 deaths in this group (mortality 6.8%). Median PIM2ROM, PICU LOS, mortality (all $P < 0.001$), and length of MV ($P = 0.035$) were significantly greater in children with secondary AP than with primary AP.

Conclusions: Unlike in adult series, children with AP rarely die. Patients with secondary AP experience more morbidity and mortality than patients with primary AP.

Key Words: children, outcomes, severe acute pancreatitis

What Is Known

- Little is known about severe acute pancreatitis (AP) in children.

What Is New

- Unlike adults, children with AP rarely die.
- In the pediatric intensive care unit, children with a secondary diagnosis of AP experience more morbidity and mortality than children with a primary diagnosis of AP.

Acute pancreatitis (AP) in children is increasing in incidence worldwide (1–5). This increase in incidence is probably multifactorial with increased awareness of the condition and hence, increased biochemical testing as well as an increase in multisystem disorders, which in turn may cause pancreatitis (1–3).

Severe AP occurs frequently in adults, with organ failure developing in approximately 40% and infected pancreatic necrosis developing in 20% of patients (6). Population-based analyses suggest that 5% to 10% of adult patients with AP die (6). Little is, however, known about severe AP in children (7). Therefore, we aimed to study a population of children who carried a discharge diagnosis of AP from a consortium of pediatric intensive care units (PICUs). This population of children may include children with both severe and nonsevere AP. We hypothesized that children who are admitted with or diagnosed as having AP in the PICU experience significant morbidity and mortality.

METHODS

Study Group and Inclusion Criteria

This was a retrospective cohort study of patients with AP as a discharge diagnosis from a PICU admission. Data were obtained retrospectively from the Virtual PICU Systems (VPS)[LLC] database. The VPS database is a multicenter database of PICUs, defined as a physical space dedicated exclusively to the care of critically ill children, and is used primarily for benchmarking and quality assessment. It has also been used to organize collaborative research among PICUs (8). Data from all PICU admissions from VPS member hospitals are entered into the VPS database (9). The database has an inter-rater reliability greater than 96%. De-identified data from 2076 discharges with a diagnosis of AP were

provided by VPS. The data included patients less than 18 years of age admitted from July 1, 2009, to June 30, 2013, from a total of 113 centers. This study was deemed exempt from review in December 2013 by the institutional review board of the Children's Hospital of Wisconsin.

Data

Data obtained from the VPS[LLC] database included age, sex, weight, primary diagnosis category, and trauma status. We also obtained data on mortality, PICU length of stay (LOS), and incidence and duration of mechanical ventilation (MV).

There are 2 well-known, validated severity of illness scores used by PICUs—the Pediatric Index of Mortality-2 (PIM2) and Pediatric Risk of Mortality III (PRISM-III) score. Both use clinical, physiologic and laboratory data obtained at PICU admission (PIM2) or during the first 24 hours of PICU admission (PRISM III). These data are used to calculate scores which in turn can be inserted into logarithmic equations to provide the predicted likelihood of mortality for a patient admitted to the PICU [the PRISM III Probability of Death (POD) or the PIM-2 Risk of Mortality (PIM2-ROM)] (10,11). Because PIM2 is a mandatory field in VPS, it is available for all patients; the PRISM III score is not a mandatory field and therefore is not available in all patients. In a previous large multi-institutional PICU study, the population with PIM2ROM and PRISM III POD >5% represented the top severity of illness category and constituted <20% of all PICU admissions (12). We also examined this group of patients in our study.

Weight is a required measure for all VPS participants. Height is not a required measure and was frequently unavailable. In addition, height is measured poorly in PICUs (13). Hence, we chose to use weight z scores to categorize children into the following categories: normal (−1.89 to 1.04), underweight (<−1.89), overweight (1.05–1.65), obese (1.66–2.33), and severely obese (>2.33).

Diagnostic Classification

VPS collects all diagnoses incurred during the PICU stay and classifies them into primary or secondary. The primary diagnosis is the principal reason for the patient's admission to the PICU and is identified at the time of discharge from the PICU. This timing enables consideration of the diagnostic results and clinical decision making in the determination of the primary reason for the patient's PICU stay. All diagnoses other than the primary diagnosis are considered secondary diagnoses. In addition, VPS also groups all diagnoses into various diagnosis categories.

Patients were classified as having primary AP if their primary discharge diagnosis was AP. If they had another primary discharge diagnosis, they were classified as having a secondary diagnosis of AP (SAP).

Outcomes

We studied mortality, PICU LOS, and incidence and duration of MV in patients with primary AP and SAP. We wished to study the outcomes that have been used to describe severity in AP in adults, that is, respiratory failure, circulatory failure, and renal failure. No measures to categorize circulatory or renal failure, however, were available for the majority of patients in this dataset.

Statistical Analysis

Descriptive statistics were used to characterize the population. Chi-square tests were used to compare the categorical variables between primary AP and SAP. Mann-Whitney nonparametric tests were used to compare the interval variables such as duration of MV and PICU LOS. SAS version 9.3 (SAS Institute, Cary, NC) and IBM SPSS Statistics version 20 (IBM SPSS Statistics, Armonk, NY) were used for analysis.

RESULTS

Between July 1, 2009 and June 30, 2013, there were a total of 360,162 PICU discharges from the web-based version of the VPS database. The data for the present study consisted of 2076 discharges with a diagnosis of AP (0.58% of total discharges) from 113 VPS centers. Of these patients, 331 had a primary diagnosis of AP, whereas 1695 had another primary diagnosis and were considered SAP. A total of 49 additional patients with both AP and SAP, and

TABLE 1. Demographic information

	Primary diagnosis of acute pancreatitis (n = 331)	Secondary diagnosis of acute pancreatitis (n = 1695)	Overall VPS population[a]	*P* for comparison of primary to secondary
Male sex, %	49.8	48.4		0.64
Age in years (median, IQR)	12.0 (7.9–15.3)	11.5 (5.5–15.2)		0.077
Racial distribution, %[a]				
White	44.1	51.5	52.1	<0.001
African-American	14.7	17.5	18.9	
Hispanic	31.3	20.4	17.2	
Asian/Pacific Islander	1.9	2.6	2.8	
American Indian	1.4	1.2	0.7	
Other	6.6	6.7	8.3	
Weight categories, %				
Underweight	17.9	22.1		<0.001
Normal weight	48.5	56.4		
Overweight	12.4	9.9		
Obese	13.3	6.3		
Extremely obese	7.9	5.3		

IQR = interquartile range; VPS = Virtual PICU Systems[LLC].
[a] This analysis was performed using patients in whom race information was available (211 patients with a primary diagnosis of acute pancreatitis, 1200 patients with a secondary diagnosis of acute pancreatitis, and 289,096 discharges from the pediatric intensive care unit).

TABLE 2. Primary diagnosis categories associated with a secondary diagnosis of acute pancreatitis

Primary diagnostic category	No. patients with a secondary diagnosis of acute pancreatitis (n = 1695)	Percentage of total	Top individual diagnoses in each category	Mortality for category, %
Endocrinologic	244	14.4	Type 1 diabetes mellitus with ketoacidosis (88.1%)	0.41
Respiratory	232	13.69	Pneumonias (36.2%), acute respiratory distress syndrome/acute lung injury (27.2%)	8.19
Infectious	199	11.74	Bacterial infections and sepsis (84.9%)	12.06
Gastrointestinal	164	9.68	Cholangitis/cholelithiasis (17.1%), gastrointestinal hemorrhage (12.8%)	1.83
Neurologic	157	9.26	Seizure disorders (43.9%)	8.92
Cardiovascular	152	8.97	Hypotension without shock (16.4%)	9.21
Injury/poisoning	136	8.02	Trauma (38.2%)	8.09
Symptoms	111	6.55	Respiratory distress (34.2%), shock not otherwise classified (21.6%)	7.21
Renal/genitourinary	78	4.6	Hemolytic uremic syndrome (41.0%), acute renal failure/acute tubular necrosis (33.3%)	3.85
Metabolic	60	3.54		5
Oncologic	58	3.42	Acute lymphoblastic leukemia (39.7%)	6.9
Hematologic	26	1.53		7.69
Orthopedic	17	1		0
Rheumatologic	15	0.88		6.67
Transplant	14	0.83		42.86
Other	32	1.89		6.25

1 SAP case with missing diagnosis information were excluded from the analysis.

The demographic information of the individuals with primary AP and SAP is shown in Table 1. The overall weight z score of children with primary AP (median 0.13 [IQR −1.39 to 1.53]) was significantly higher than the median weight z score of children with SAP (−0.25, IQR −1.66 to 0.84; ($P < 0.001$). The primary diagnostic categories along with the major diagnoses that are predominant in each category are shown in Table 2.

Severity of Illness

All children had PIM-2 scores available, whereas only 1587 children (305 with primary AP and 1282 with SAP) had PRISM III scores available. In primary AP, median PIM2ROM was 0.96% (IQR 0.8%–1.4%), whereas in SAP, median PIM2ROM was 1.1% (IQR 0.8%–4.0%, $P < 0.001$). Similarly, in primary AP, median PRISM III POD was 0.8% (IQR 0.4%–2.0%), whereas in SAP, median PRISM III POD was 1.0% (IQR 0.4%–4.0%, $P = 0.021$).

We also assessed the number of children with a PIM2ROM or a PRISM III POD $\geq 5\%$. In children with primary AP, 1.5% of children had a PIM2ROM $\geq 5\%$ versus 14.7% with SAP ($P = 0.0002$). Similarly, in children with primary AP, 2.1% of children had a PIM2ROM $\geq 5\%$ versus 18.5% with SAP ($P = 0.0004$).

Outcomes

Only 1 of 331 patients with primary AP died (mortality 0.3%), whereas there were 115 deaths in the SAP group (mortality 6.8%; $P < 0.001$). The mortality risk ratio (for secondary AP compared with primary AP) was 22.46 (95% confidence interval 3.15–160.22). In patients in the SAP group, we attempted to ascertain the primary diagnostic categories in which mortality was highest and further analyzed deaths in the primary diagnosis categories with at least 50 patients in each category. In these categories, deaths occurred most frequently in the infectious (12.1%), cardiovascular (9.2%), respiratory (8.2%), and injury/poisoning (8.1%) categories.

A total of 55 children with primary AP (16.6%) and 711 children (42.0%) with SAP required MV. Children with primary AP required MV for a median of 3.8 days (IQR 1.0–9.3), whereas children with SAP required MV for a median of 5.8 days (IQR 1.8–14.0, $P = 0.035$).

In children with primary AP, PICU LOS stay was a median of 2.95 days (IQR 1.53–5.90), whereas in children with SAP, PICU LOS was a median of 4.43 days (IQR 1.84–11.22, $P < 0.001$).

In children with a primary diagnosis of AP, PICU LOS, the percentage of children requiring MV and length of MV were not associated with race or weight status (data not shown).

DISCUSSION

In our study, we found that approximately 1 in 200 children admitted to a PICU carried a diagnosis of AP. Of these children, the vast majority (84%) developed pancreatitis in association with or secondary to another underlying condition. In our multicenter pediatric cohort, AP was not as severe as AP is in adults, with much lower mortality and morbidity (14–18). Whereas population-based mortality rates in adults are between 5% and 10%, adults with severe AP have mortality rates between 15% and 30% (16). Children with a primary diagnosis of AP were less sick than those with SAP. The racial distribution of children with primary AP was different from children with secondary AP. This may be because of an increased incidence of primary AP in Hispanic children. This is supported by the data that link Hispanic ethnicity with biliary pancreatitis (7). In addition, in our study the weight distribution of children with primary AP was different from children with secondary AP; this was because of an increase in overweight and obese children in primary AP and underweight children in secondary AP. In other studies, overweight and obesity have been linked to the increasing occurrence of AP in adults (19,20) and possibly in children (7). In adults, obesity has been associated with

severe AP (21,22). This association was also suggested by a smaller pediatric study (23). Our data do not show any associations between weight status or race and severity in primary AP.

Clearly, more children in the PICU have AP associated with other conditions than having primary AP. Some of these conditions have been associated with pancreatitis, most importantly trauma, drugs and toxins, biliary disease, and diabetes. We can speculate that some of the patients with acute lymphocytic leukemia received L-asparaginase and that some of the patients with seizures received valproate (24). With regard to the rest of the conditions, it is unclear whether there is a clear association with the primary condition or whether pancreatitis is associated with or an end result of critical illness. For instance, the diagnosis of AP in diabetic ketoacidosis (DKA) can be tricky. DKA is associated with AP in approximately 10% to 15% of adults (25) and 2% of children (26), but nonspecific elevations of lipase and amylase can occur in DKA, as well (25,26). It is unclear as to what degree of rigor was used in making the diagnosis of AP in patients with DKA or in any of the patients in this cohort. Our data also show that a variety of multisystem disorders are associated with AP and this is in accordance with other studies (5,27,28). Finally, hemolytic uremic syndrome, which has been associated with AP in other pediatric studies, is seen in children with AP in the PICU (27–29).

Our data show that children with SAP are sicker at presentation to the PICU (as assessed by PIM2 and PRISM III) than children with primary AP. Unlike adults, children rarely die from primary AP. SAP, however, is associated with significant mortality. Mortality in AP in children has ranged from 0% to 26.7% (2–5,27,28,30–33). The 2 studies with the highest mortality rates, 21% and 26.7% were from 1978 and 1988, respectively, and probably reflect a prior era of medical care (28,33). The mortality rates in our study of 0.3% for primary pancreatitis and 6.8% for secondary AP are comparable with several newer studies (2–5,27,30–32). In most of the above studies, it is difficult to separate out mortality in primary AP versus SAP; however, most deaths were because of multisystem disease rather than AP (2–5,27,30).

The children with a primary diagnosis of AP and SAP experienced significant morbidity. Both the length of hospitalization and the need for and length of MV were longer in the SAP group. Because this is the first study of such a large number of critically ill children with AP, there are no other studies to which we can compare our findings. The median LOS for children with uncomplicated AP is between 5 and 8 days (4,5,34,35). Adults with mild AP also have a similar hospital LOS (36). We were unable to obtain hospital LOS on our patients. One pediatric study reported a median LOS for mild and severe AP to be 13 and 20 days, respectively (31).

From our data, it is difficult to discern what proportion of our patients had severe AP. Severe pancreatitis is defined as the presence of either local complications such as pseudocyst formation or systemic complications such as organ failure (37). Adult studies of patients with primary AP strongly suggest that systemic complications and infection are the main causes of mortality. Local complications cannot be gleaned from our data. Based on the incidence of MV, at least 17% of our patients with a primary diagnosis of AP and 42% of our patients with SAP had systemic complications of AP. One important caveat is that it is not clear that the AP caused the need for MV, especially in our patients with secondary AP. We were unable to obtain data about circulatory or renal failure in our patients.

Our study has several strengths. This is the largest cohort study of children with AP in any setting. Our study also has gathered data on children who are sicker than the standard child with AP. Our

data on severity of illness, mortality, and MV are likely to be extremely accurate.

There are several important limitations of this study. First, it is a retrospective analysis and suffers from the limitations inherent in such a study design. In addition, the VPS database was designed to study outcomes in the PICU and not to study AP. A major limitation of this study is the diagnosis of AP in these patients. The diagnosis is typically made using a combination of clinical symptoms and either biochemical or imaging parameters. In many of these children, clinical symptoms may not have been apparent as they were too sick to complain of abdominal pain. Both over- and underdiagnosis is likely. It is certain that there were children in the PICU who had pancreatitis that were not diagnosed; there were also probably children who were diagnosed as having AP based solely on mildly elevated amylase and lipase. In the sicker patients, the diagnosis of AP was probably based on the biochemical changes as clinical symptoms would have been lacking and many of these patients may not have been transported to radiology units for confirmatory imaging. This may have been appropriate because requiring clinical, biochemical, and radiologic evidence of AP underestimates disease incidence, because patients can have AP with only biochemical changes (38–40). There is, however, a concern that including patients with clinical and biochemical evidence of AP without radiologic changes may overestimate the incidence of AP, but this was not seen in a large adult study. Some of these patients with purely an elevation of serum amylase or lipase without radiological evidence may have had nonpancreatic diseases (38,41). In general, imaging in children with AP is not recommended unless there is a complication (42). Because PICU admission was certainly necessitated by a complication, many of these children could have, however, been subjected to imaging.

Although there are limitations to registry data, the integrity and validity of the data and possibility of sampling bias are addressed through the use of uniform operational definitions, uniform data collection, rigorous abstractor training and competency-based certification, and detailed periodic reabstraction. Sampling bias in VPS is minimized through the use of strict inclusion and exclusion criteria, comprehensive methods to verify data completeness, and large sample size. It is, however, possible that the existing VPS data elements failed to capture unmeasured confounders.

In conclusion, AP is an uncommon occurrence in the PICU. Children with AP are not as sick as their adult counterparts with the same condition and children with primary AP rarely die (0.3%). Children with SAP have significant mortality (6.8%). Both children with primary AP and SAP experience significant morbidity.

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