

Classification of Acute Pancreatitis in the Pediatric Population: Clinical Report From the NASPGHAN Pancreas Committee

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ABSTRACT

Introduction: Acute pancreatitis (AP) is an emerging problem in pediatrics, with most cases resolving spontaneously. Approximately 10% to 30%, however, are believed to develop “severe acute pancreatitis” (SAP).

Methods: This consensus statement on the classification of AP in pediatrics was developed through a working group that performed an evidence-based search for classification of AP in adult pancreatitis, definitions and criteria of systemic inflammatory response syndrome, and organ failure in pediatrics.

Results and Discussion: Severity in pediatric AP is classified as mild, moderately severe, or severe. Mild AP is defined by AP without organ failure, local or systemic complications, and usually resolves in the first week. Moderately SAP is defined by the presence of transient organ failure that resolves in no >48 hours, or local complications or exacerbation of comorbid disease. SAP is defined by persistent organ failure that lasts <48 hours. The presence of systemic inflammatory response syndrome is associated with increased risk for persistent organ dysfunction. Criteria to define organ failure must be pediatric- and age-based.

Conclusions: Classifying AP in pediatrics in a uniform fashion will help define outcomes and encourage the development of future studies in the field of pediatric pancreatitis.

Key Words: consensus statement, mild acute pancreatitis, moderately severe acute pancreatitis, organ failure, pediatrics, severe acute pancreatitis, systemic inflammatory response syndrome

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Acute pancreatitis (AP) is increasing in the pediatric population across the world, with a reported incidence of up to 13/100,000 (1–4). Despite this more frequent presentation, the natural history of AP is poorly understood and no good predictors

What Is Known

- Acute pancreatitis, acute recurrent pancreatitis, and chronic pancreatitis defined for pediatric patients.
- Severity of acute pancreatitis has been defined for adult patients.
- There are no pediatric-specific classification schemes of severity for pediatric patients with acute pancreatitis.

What Is New

- Pediatric acute pancreatitis is classified into mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis using pediatric-based criteria of organ dysfunction and systemic inflammatory response.

determine progression to severe disease. In most pediatric cases, AP resolves and patients have no further complications related to pancreatitis. In a subset of children, however, complications from local pancreatic and systemic inflammatory responses occur and may result in severe disease (5–7). It is important that we recognize and classify severe acute pancreatitis (SAP) in children, as this has been shown in adults to have prognostic implications and helps categorize patients to guide clinical management (8–10). Currently, based on the available literature and without a consensus definition for SAP, 15% to 34% of pediatric patients develop severe disease

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(6,7,11,12). A recent editorial emphasized the need to define the severity of AP in pediatrics to develop a framework to better understand pancreatitis and as a foundation for future studies to investigate therapeutic efficacy and outcomes (13).

Although adult pancreatology groups continue to review and update definitions of AP, with the most recent international efforts being published as recently as 2013 (14), the same effort has not occurred in pediatrics. To address this apparent knowledge gap, we propose the first pediatric specific classification of AP to be used in future pediatric AP studies.

METHODS

The AP Classification working group consisted of the main authors-members (M.A.H., S.K., F.S., S.W.) and Chair (V.M.) of the NASPGHAN (North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition) Pancreas Committee in 2016, and 2 adult pancreatologists (P.B. and D.C.). Other members of the NASPGHAN Pancreas Committee reviewed and commented upon the manuscript before the final version being approved. These members are listed in the acknowledgment section.

The main authors, pediatric gastroenterologists with expertise in pancreatology, searched the literature on the epidemiology of AP and SAP, and documented definitions of SAP according to previously published studies. Key words included definitions of AP and SAP. English language adult and pediatric literature was reviewed. Regular calls and email correspondences were conducted between the authors and the committee chair, VM. The manuscript was then shared with 2 preselected adult expert pancreatologists involved in determining classification of AP in the adult population. Members of the NASPGHAN Pancreas Committee were invited to review the manuscript and encouraged to respond, to develop the document into an expert opinion consensus statement that was based on published literature review, and agreed-upon by a larger group of pediatric gastroenterologists with interest and expertise in pancreatology.

RESULTS AND DISCUSSION

Background

Background Literature

One of the main factors that has hindered progress in the study of pancreatitis in children is the lack of uniform classification of AP used in different pediatric studies (5). Unfortunately, many pediatric studies have failed to address this important issue to date. DeBanto and the Midwest Multicenter Pancreatic Study Group was the first group to define SAP in children in 2002 (11). They derived the criteria from the adult international consensus for SAP, based on the Atlanta Classification of 1991 (15). Significant differences, however, are apparent in the clinical presentation and etiology of pancreatitis between children and adults, with adults having a large proportion related to either biliary (gallstones) or alcohol ingestion, whereas for children, the main etiologies are more diverse including anatomic variants, drugs/toxins, infectious, trauma, biliary/obstructive, metabolic, genetic, and “idiopathic” causes (5). Thus, the Atlanta classification based upon adult literature may not be appropriate to define severity of pediatric AP.

Despite the known limitations of the Atlanta Criteria, the Midwest Multicenter Pancreatic Study Group defined SAP as meeting at least one of the following criteria: death as a result of the disease, surgery to the pancreas (resection or drainage procedures), development of pseudocyst, abscess or necrosis, or development of organ dysfunction (systolic blood pressure <90 mmHg, PaO₂ <60, creatinine >2 mg/dL, or gastrointestinal (GI) bleeding >500 mL/24 hours).

Several subsequent retrospective pediatric studies have used similar criteria with minor differences (6,7,12,16). Table 1 summarizes how various pediatric study groups defined SAP and the methods by which the information was extracted for the clinical studies.

A major limitation in applying adult criteria in pediatric cases has been in defining organ dysfunction in children. Circulatory dysfunction based on a systolic blood pressure <90 mmHg will overestimate SAP, especially in the younger age groups wherein normal systolic blood pressure may be <90 mmHg. As an example, if a 5-year-old girl patient who is 5th percentile for height presented with AP and had a systolic blood pressure of 89 mmHg, she would be classified as having severe AP, when in fact her systolic blood pressure would actually be at 50th% (17) and should be considered normal. Similarly, using creatinine >2 mg/dL to define renal dysfunction will likely underestimate kidney injury, as this value is also highly age-, weight/height-, and muscle mass-dependent. Thus, in certain cases, especially in younger children, kidney injury might be present at creatinine values lower than 2 mg/dL, but organ dysfunction criteria for SAP not be fulfilled. For clinical applications, the absolute change in creatinine value from an individual patient's baseline, if known, would be the more appropriate method to define kidney injury (18) because even a modest increase (eg, by 0.3 mg/dL) in baseline creatinine is a risk factor for mortality in adult and pediatric patients (19–21).

Other criteria may also be seldom fulfilled because of differences between pediatric and adult responses to AP. GI bleeding related to pancreatitis is rare in children (22), and even more rarely would blood volume losses exceed 500 mL/24 hours (which would be an extremely significant volume in a toddler), making this criterion poorly applicable to the pediatric population. Severe GI bleeding is a rare complication even in adults and is typically accompanied by other organ failure. Owing to this, GI bleeding was eliminated as criterion for SAP in the revised adult AP Atlanta Criteria published in 2013 (14). Respiratory complications can be common in SAP because of third spacing and ventilation-perfusion mismatch. Most children, however, do not undergo arterial puncture for obtaining arterial blood gases, unless they are in the intensive care unit (ICU) and being monitored via arterial access. Using PaO₂ as sole criteria for identifying respiratory complications will therefore exclude such patients. Most pediatric patients, however, can be identified as having respiratory compromise by increased O₂ requirement and by having imaging findings of pulmonary edema or pleural effusion. Pulmonary findings of edema or effusion alone would not qualify for organ failure unless it caused respiratory distress or increased oxygen requirements in a child. These findings may be useful especially in cases wherein PaO₂ is not available.

Definition of Acute Pancreatitis in Pediatrics

AP in children has been previously defined as having the presence of at least 2 of the following 3 criteria (23): abdominal pain compatible with pancreatic origin, amylase and/or lipase at least 3 times upper limits of normal, and imaging findings suggestive/compatible with pancreatic inflammation.

Definitions of Organ Dysfunction and Systemic Inflammatory Response in Pediatrics

The “International Pediatric Sepsis Consensus Conference” in 2002 (18) established criteria to define “organ dysfunction” in children. Although the primary goal was to develop definitions for

TABLE 1. Criteria for severe acute pancreatitis in previous pediatric studies

	De Banto et al (2002) (11)	Suzuki et al (2008) (16)	Lautz et al (2011) (7)	Coffey et al (2013) (6)	Szabo et al (2016) (12)
Death	Retrospective review of patient records identified patients who died during admission [†] *	Retrospective review of patient records identified patients who died during admission [†] *	Retrospective review of patient records identified patients who died during admission [†]	Retrospective review of patient records identified patients who died during admission [†] *	Retrospective review of EMR identified patients who died during admission [†]
Surgery on the pancreas	*	*	ICD-9 52.11–12, ICD-9 52.01, 52.4–7, 52.95–96, 52.99	*	Retrospective review of imaging studies in the EMR identified patients who had developed such complications [†]
Local complication (pseudocyst, abscess, necrosis)	*	*	ICD-9 577.2 and confirmed by imaging	*	
Organ dysfunction (≥1)					
Circulation	Systolic BP <90 mmHg	Systolic BP <90 mmHg	Shock = need for pressors	Systolic BP <90 mmHg	*
Renal dysfunction	Creatinine >2 mg/dL	Creatinine >2 mg/dL	Acute renal failure: ICD-9 584.5 or 584.9 (US criteria) or creatinine >2 mg/dL		*
GI bleed	>500 mL/24 h	>500 mL/24 h	Severe GI bleed		
Respiratory complications	PaO ₂ <60 mmHg	PaO ₂ <60 mmHg	ICD- 518.0 (pulmonary collapse), 518.81 (acute respiratory failure), 518.82 (acute respiratory distress) or PaO ₂ <60	PaO ₂ <60 mmHg, or O ₂ requirement with radiologic findings	Pulmonary edema, pleural effusion on radiologic studies, or requiring supplemental O ₂
Intensive care unit admission (primarily for pancreatitis)				*	*

For each study, ≥ 1 of the listed criteria had to be met to consider a pancreatitis case severe. Empty cell indicates that the criterion was not addressed in the manuscript.
 BP = Blood pressure; EMR = electronic medical records; GI = gastrointestinal; ICD = International Classification of Diseases.
 *The Manuscript does not specify how the criteria were decided.
[†]The Manuscript specifies how the criteria were decided.

TABLE 2. Criteria of organ dysfunction as per the International Pediatric Sepsis Consensus (18)

Cardiovascular dysfunction	Respiratory dysfunction	Renal dysfunction
<p>≥1 of the following despite administration of isotonic intravenous fluid bolus ≥40 mL/kg in 1 h</p> <p>Decrease in BP (hypotension) <5th percentile for age or systolic BP <2 SD below normal for age</p> <p>Need for vasoactive drug to maintain BP in normal range (dopamine >5 μg · kg⁻¹ · min⁻¹ or dobutamine, epinephrine, or norepinephrine at any dose)</p> <p>Two of the following:</p> <p>Unexplained metabolic acidosis (BD >5.0 mEq/L)</p> <p>Increased arterial lactate >2 × ULN</p> <p>Oliguria: urine output <0.5 mL · kg⁻¹ · h⁻¹</p> <p>Prolonged capillary refill: >5 s</p> <p>Core to peripheral temperature gap >3°C</p>	<p>≥1 of the following in absence of preexisting lung disease or cyanotic heart disease</p> <p>PaO₂/FIO₂ <300 in absence of cyanotic heart disease or preexisting lung disease</p> <p>(2) PaCO₂ >65 torr or 20 mmHg over baseline PaCO₂</p> <p>(3) Proven need or >50% FIO₂ to maintain saturation ≥92%</p> <p>(4) Need for nonelective mechanical ventilation</p>	<p>(1) Serum creatinine ≥2 times upper limit of normal for age or 2-fold increase in baseline creatinine</p>

BD = base deficit; BP = blood pressure; SD = standard deviation; ULN = upper limits of normal.

pediatric sepsis, multiorgan dysfunction syndrome (MODS) was defined as part of the defining criteria. Hepatic dysfunction, neurologic changes, and hematologic dysfunction have not been considered hallmarks of SAP and are not part of the criteria in the revised Atlanta Criteria, or in previous pediatric studies (6,7,11,14,16). Adult data indicate that patients who develop organ failure within the first few days of the AP presentation have greater mortality (24–27). Table 2 lists the proposed criteria for organ dysfunction (derived from the definitions accepted in the International Pediatric Sepsis Consensus (18)) to be used in the classification of pediatric AP as mild, moderate, or severe.

Definitions of Systemic Inflammatory Response Syndrome in Pediatrics

According to published data in adults, the presence of systemic inflammatory response syndrome (SIRS) carries an increased risk for developing persistent organ dysfunction (26–28). The main components of SIRS as defined in the adult literature include changes in body temperature, heart rate, respiratory rate, and leukocyte count abnormalities (29). Before 2002, various definitions were being used throughout the pediatric medical literature. The International Pediatric Sepsis Consensus Conference held in 2002 developed the first consensus definitions for SIRS, published in 2005 (18). This expert opinion consensus included age-based criteria for each of the parameters to reflect the reality that normal physiologic values for these change with age. Numerous biomarkers have since then been proposed to aid in the diagnosis of SIRS such as elevated sedimentation rates, C-reactive protein, interleukin-6, and procalcitonin. Although some of these biomarkers are sensitive, they lack specificity and thus have not yet been included in the current definition of SIRS nor studied in pediatrics. The work in this field is ongoing (30–32). Table 3 summarizes the criteria for SIRS based on the International Pediatric Sepsis Consensus Conference (18). Cardiovascular, respiratory, and renal dysfunction can develop because of severe SIRS, and all have the potential to develop into organ failure.

Definitions of “Local” Complications in Pediatric Pancreatitis

Local complications described in the literature include peripancreatic fluid collections, necrotic fluid collections, pancreatic and peripancreatic necrosis (sterile or infected), and development of pseudocysts and walled-off necrosis (sterile or infected). A pseudocyst, a mature fluid collection containing no solid material surrounded by a defined wall, usually does not form in <4 weeks (10,14). Hence, this complication is not useful in the acute determination of severity, but can be used retrospectively in the description of severity of an attack of AP. Other less-common complications include gastric outlet and duodenal obstruction, and splenic and portal vein thromboses. Some of these complications may not/do not develop within the first few days of the onset of pancreatic injury, but may manifest later. Recurrence of abdominal pain, development of fever, and new and progressive increase in serum pancreatic enzyme levels could be signs indicating the development of such complications. The exact characteristics of these changes are best investigated by cross-sectional imaging (such

TABLE 3. SIRS criteria as per the 2002 International Pediatric Sepsis Consensus (18)

<p>The presence of minimum 2 of the following 4 criteria (one of which must be abnormal temperature or leukocyte count):</p> <p>Temperature of >38.5°C or <36°C.</p> <p>Leukocyte count elevated or depressed for age or >10% immature neutrophils.</p> <p>Elevated heart rate >2SDs above normal for age in the absence of external factors such as associated fussiness, crying, or irritability; or unexplained persistent elevation over a 0.5- to 4-h time period. For children younger than 1 y: decreased heart rate <10th percentile for age in the absence of external factors such as vagal stimulation or medications; or otherwise unexplained persistent depression over a 0.5-h time period.</p> <p>Mean respiratory rate >2 SD above normal for age or requiring mechanical ventilation for an acute process not related to underlying disease or general anesthesia.</p>
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SD = standard deviation.

as computed tomography [CT] imaging with intravenous contrast or magnetic resonance imaging (33,34).

Definitions of “Systemic” Complications in Pediatric Pancreatitis

Banks et al (14) defined systemic complications in adult AP as: “exacerbation of pre-existing co-morbidity, such as coronary artery disease or chronic lung disease, precipitated by the acute pancreatitis”. Systemic complications in pediatric AP would similarly include symptoms of exacerbation of underlying previously diagnosed chronic illness such as of chronic lung disease, heart disease, or renal disease.

Definitions of Severe Acute Pancreatitis

Atlanta Classification of Severe Acute Pancreatitis in Adults

SAP was initially defined by the development of organ failure (10,14). The Atlanta Classification was later revised in 2012 and it subdivided SAP in adults into: *moderately severe AP* and *severe AP* (14). Moderately SAP included evidence of local or systemic complications in the absence of “persistent” organ failure (<48 hours). SAP was defined by “persistent” organ failure (>48 hours). Organ failure in adults was defined by a score of ≥2 based on the modified Marshall scoring system (14,35). The modified Marshall scoring system includes parameters regarding respiratory, renal, and cardiovascular status. Unfortunately, this scoring system cannot be readily applied to children because it uses adult based metrics and laboratory values.

Proposal: Classification of Acute Pancreatitis in Pediatrics

We propose the following definitions of severity in pediatric AP based on the previously published studies in children and adults.

Subsequent to establishing a diagnosis of AP in a child, severity grading may be assigned. Severity of AP in pediatrics would be classified (as in adults) as mild, moderately severe, or severe:

- *Pediatric mild AP*: AP that is not associated with any organ failure, local or systemic complications, and usually resolves within the first week after presentation. This is the most common form of pediatric AP.
- *Pediatric moderately severe AP*: AP with either the development of transient organ failure/dysfunction (lasting no >48 hours) or development of local or systemic complications. Local complications would include development of (peri) or pancreatic complications including fluid collections or necrosis. Please refer to below for further details. Systemic complications would include exacerbation of previously diagnosed co-morbid disease (such as lung disease or kidney disease).
- *Pediatric severe AP*: AP with development of organ dysfunction that persists >48 hours. Persistent organ failure may be single or multiple, and may develop beyond the first 48 hours of presentation

The Algorithm (Fig. 1) categorizes severity of pediatric AP. While Although is not a criterion in the definition of SAP, the presence of SIRS increases the risk of persistent organ failure in this patient population. Careful attention should be paid to age and weight-based values for defining organ dysfunction. At the current time, we recommend using the criteria of organ dysfunction as per the International Pediatric Sepsis Consensus to define organ dysfunction (18). Children with organ dysfunction or failure should be monitored to determine whether the organ failure persists beyond 48 hours. It is important to note that although organ dysfunction typically develops early in the course of AP, a child should be periodically reevaluated throughout the entire hospitalization for development of any organ dysfunction. The moderately severe AP category calls attention to patients who are sicker than mild AP and require longer hospitalization than mild AP, but are not as sick as severe AP and unlikely to have severe adverse outcomes described

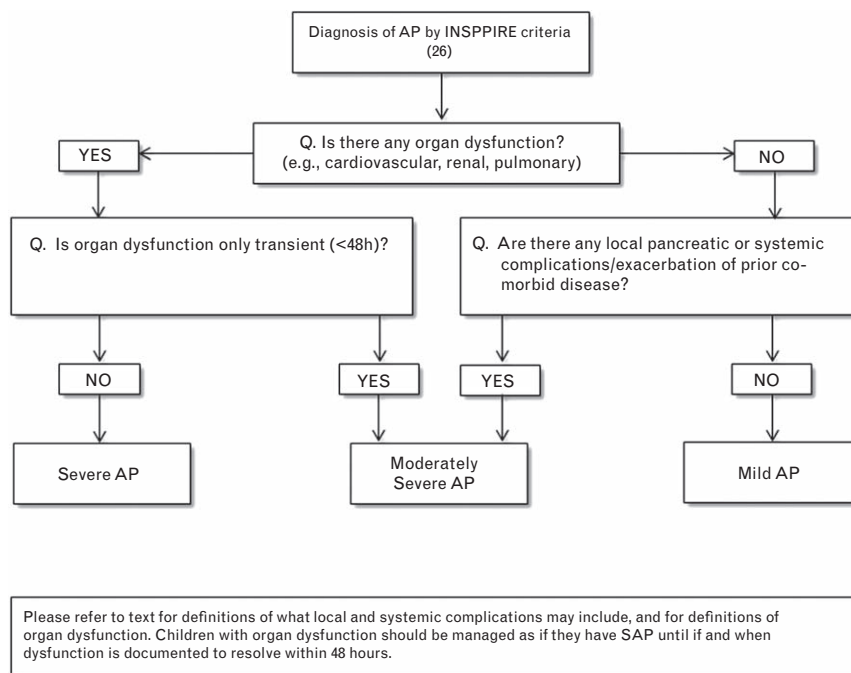


FIGURE 1. Algorithm to categorize severity of pediatric acute pancreatitis.

in severe AP. “Local complications” such as fluid collections typically will be symptomatic if they are significant in the classification scheme above. For example, patients with ongoing symptoms such as pain requiring narcotics, fever, or elevated white blood cell count undergoing detailed imaging through a CT scan after 3 to 6 days looking for a complication would be moved up to moderately SAP category on the basis of symptoms and CT findings of a pancreatic fluid collection. In contrast, imaging performed at admission without particular symptomatology demonstrating fluid in a patient who improves quickly and is discharged within 3 to 4 days should be disregarded, and the patient should be included in the mild AP category. From a radiological stand point, any volume of peripancreatic fluid greater than mild peripancreatic inflammation or edema (which manifests as haziness or reticular strands of fluid in the surrounding tissue) is considered an acute fluid collection and should be measured.

CONCLUSIONS

Widely accepted definitions for pediatric AP would allow us to stratify patients accurately when measuring outcomes in pediatric AP studies. For the purpose of stratifying patients, we recommend categorizing pancreatitis into mild, moderately severe, or severe AP. Mild AP is pancreatitis without organ failure, local or systemic complications and usually resolves in the first week. Moderately SAP is defined by the development of transient organ failure, local complications, or exacerbation of co-morbid disease. SAP is defined as pancreatitis with persistence of organ failure beyond >48 hours. Criteria to diagnose organ failure need to be strictly pediatric-based. The main difference between moderately SAP and SAP relates to the duration of organ failure.

This proposed classification of AP will help clinicians and researchers categorize cases of childhood AP into subgroups and provide common grounds for outcomes research and comparative effectiveness studies, and to help understand disease evolution and identify points of medical intervention that could improve outcome. Better prediction models are needed. Identifying early features of disease will allow clinicians to develop prognostic tools and scoring systems to stratify patients who are prone to developing a severe course, thereby identifying patients who are likely to require intensive care, should be transferred to a more specialized pediatric center, or are likely to require the expertise of specialists and a multidisciplinary care approach. The creation of this common language will also foster future research studies. We anticipate that review of research using these definitions will help redefine and refine pediatric AP classifications in upcoming years, similarly to the exercise that has occurred for adult AP via the Atlanta classification and its 2012 revision.

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