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The Management of Acute Pancreatitis in the Pediatric Population: A Clinical Report from the NASPGHAN Pancreas Committee

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Abstract

Background—While the incidence of acute pancreatitis (AP) in children is increasing, management recommendations rely on adult published guidelines. Pediatric-specific recommendations are needed.

Methods—The NASPGHAN Pancreas committee performed a MEDLINE review using several pre-selected key terms relating to management considerations in adult and pediatric AP. The literature was summarized, quality of evidence reviewed, and statements of recommendations developed. The authorship met to discuss the evidence, statements, and voted on recommendations. A consensus of at least 75% was required to approve a recommendation.

Results—The diagnosis of pediatric AP should follow the published INSPPIRE definitions (by meeting at least two out of three criteria: (1) abdominal pain compatible with AP, (2) serum amylase and/or lipase values 3 times upper limits of normal, (3) imaging findings consistent with AP). Adequate fluid resuscitation with crystalloid appears key especially within the first 24h. Analgesia may include opioid medications when opioid-sparing measures are inadequate. Pulmonary, cardiovascular, and renal status should be closely monitored particularly within the first 48 hours. Enteral nutrition should be started as early as tolerated, whether through oral, gastric, or jejunal route. Little evidence supports the use of prophylactic antibiotics, anti-oxidants, probiotics, and protease inhibitors. Esophago-gastro-duodenoscopy, endoscopic retrograde cholangiopancreatography and endoscopic ultrasonography have limited roles in diagnosis and management. Children should be carefully followed for development of early or late complications as well as recurrent attacks of AP.

Conclusions—This clinical report represents the first English-language recommendations for the management of pediatric AP. Future aims should include prospective multi-center pediatric studies to further validate these recommendations and optimize care for children with AP.

Keywords

Monitoring; nutrition; fluid; analgesia; antibiotic; enteral; parenteral; probiotics; antioxidants; protease inhibitors; endoscopy; endoscopic retrograde cholangiopancreatography (ERCP); endoscopic ultrasonography (EUS); surgery

INTRODUCTION

Acute pancreatitis (AP) has been increasingly diagnosed in children in recent decades (1–3). A variety of etiologies can result in AP in children, including structural/anatomic, obstructive/biliary, trauma, infections, toxins, metabolic, systemic illness, inborn errors of metabolism, and genetic predispositions. These are a much more prevalent compared with adult AP, when biliary and alcoholic causes are well-recognized to be the two primary AP risk factors(4).

Most of the literature regarding management of AP describes *adult* experience. Recommendations for fluid resuscitation, prognosis based on markers of severity/signs of multi-organ failure, and management thereof are all based on adult criteria and experience, and reflect experience with etiologies leading to AP in adults. For the reasons listed above, adult recommendations cannot be applied directly to the pediatric population diagnosed with AP.

Although pediatric pancreatologists may be consulted during an AP hospitalization, a child will typically be initially and primarily handled by a pediatrician and/or a general pediatric gastroenterologist at the first episode of AP. Thus broader awareness of available published evidence/gaps/recommendations for managing both the early and later phases of AP in children are needed.

The aims of the current clinical report consist mainly to review published evidence for management of AP in children, compare and contrast pediatric to adult literature, identify gaps and limitations in the available literature and knowledge, and make recommendations for providers for a unified approach to help guide clinical management of children with AP.

METHODS

The working group involved in the development of this NASPGHAN clinical report included members of the NASPGHAN Pancreas Committee in early 2016, under the leadership of the Pancreas Committee chair (VM).

Three subgroups were created, headed by the three co-first authors (MAEH, SK, AQ), who provided guidance on the main topics of interest to be sub-divided for thorough review of the available literature. Topics were selected ahead of time through group discussions. Keywords included pediatrics, acute pancreatitis, diagnosis, management, intravenous fluids, enteral nutrition, parenteral nutrition, pain management, antibiotics, probiotics, antioxidants, anti-proteases, endoscopy, endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), surgery, outcomes, and complications.

All available adult and pediatric publications were reviewed after each subgroup conducted Medline searches using the above keywords to generate output to end date July 2016. All English literature was reviewed, and one foreign language (5) document was translated and reviewed(5). Regular calls and email correspondences were conducted between the subgroup leaders and committee chair. Section paragraphs were written by subgroup members. Subsections were assembled by the subgroup leaders and senior author. Tentative summary statements and recommendations were written. The first manuscript draft was circulated among all authors in August–September 2016.

A face-to-face meeting was held at the 2016 World Congress of Pediatric Gastroenterology, Hepatology and Nutrition in Montreal, QC, Canada in October 2016. Each subgroup presented pertinent literature review, and proposed statements to vote upon for each element being considered. The evidence presented and summary statements/recommendations were discussed and modified based on the feedback of attendees. Strength of scientific evidence was reviewed.

It had been initially anticipated that the group would grade the quality of evidence to support each recommendation, utilizing the GRADE system (6). However, upon review of the literature by the group at the World Congress, it was deemed that the overall quantity and quality of pediatric data were so limited that it was decided that all recommendations could only be stated to have either (1) “low” quality of evidence- meaning that further research is likely to impact our confidence in the estimate of effect and likely to change the estimate, or (2) “very low” quality of evidence so that any estimate of effect is uncertain. Hence recommendations were not individually labelled with quality of evidence. Subsequent to group discussion, each summary statement was voted upon, using a 5-point scale (5- strongly agree; 4- agree; 3- neutral: neither agree nor disagree; 2- disagree; 1- strongly disagree). It had been agreed ahead of time that consensus could only be reached if at least 75% of the participants voted “4” (agree) or “5” (strongly agree) on a statement. Voting was anonymous, and no justification was requested for what response category was selected. Members that could not physically be present were encouraged to participate by phone/by internet during the process. For those that could not participate via these methods, the manuscript draft and recommendations were re-circulated by email, with request to vote upon each statement within one-week.

Subsequent to the October 2016 face-to-face meeting, subgroup leaders re-edited their respective manuscript sections, summary and statement wording was finalized, and the updated draft was circulated amongst all authors for a second round of voting via internet in February 2017. The same 5-point scale was utilized, and authors were instructed to answer within 14-days Twenty-four authors were eligible to vote. Results were tabulated and included within the manuscript. The updated draft of the manuscript was recirculated to all participating committee members for further review and editing until a final manuscript draft was agreed upon by all authors. The final version was reviewed and approved by the NASPGHAN Council.

RESULTS

1. INITIAL EVALUATION AND DIAGNOSIS OF PEDIATRIC ACUTE PANCREATITIS

Recent studies estimate the incidence of acute pancreatitis (AP) at ~1/10,000 children per year (2, 7), an incidence approaching that of adults. There are no evidence-based diagnostic guidelines for AP in children. The INSPPIRE (**I**nternational **S**tudy Group of **P**ediatric **P**ancreatitis: **I**n Search for a **CuRE**) definition of pediatric AP is an expert definition modeled after the Atlanta criteria in adults (8). As per INSPPIRE criteria, a diagnosis of AP requires at least 2 of the following: (1) abdominal pain compatible with AP, (2) serum amylase and/or lipase values ≥ 3 times upper limits of normal, (3) imaging findings consistent with AP (9, 10). INSPPIRE or other criteria do not address phases (early or late) of AP in children or types (interstitial edematous pancreatitis, necrotizing pancreatitis, infected pancreatic necrosis) or severity of AP (mild, moderate or severe AP with multisystem organ failure).

Pediatric AP diagnosis is typically suspected clinically with compatible symptom presentations, and confirmed by laboratory and/or radiological studies. Abdominal pain and/or irritability are the most common findings of AP in children, followed by epigastric tenderness, nausea and vomiting (11, 12). In infants and toddlers, symptoms may be subtle; therefore, the diagnosis requires a high level of suspicion. Biliary/obstructive factors, medications and systemic diseases are the main causes of childhood AP (1, 4, 9, 12–23) and knowledge of these possible etiologies will guide the initial investigations.

The percentage of children who develop “severe” acute pancreatitis is variable in published series (6–34), but children with AP in general have a mild course (11, 24, 25). In a subset of patients, AP may have a severe course (8), but no established clinical tools predict this outcome. The scoring systems to assess severity of AP in adults (Ranson, Glasgow, modified Glasgow, Bedside Index of Severity in Acute Pancreatitis (BISAP) and Acute Physiology and Chronic Health Evaluation II (APACHE II)) are not easily applicable to children for several reasons(26). DeBanto’s pediatric acute pancreatitis score (PAPS) (27) was assessed in children but has low sensitivity and requires 48 hours for risk prediction. Likewise, the computed tomography severity index (CTSI) or Balthazar score (28), relies on radiologic appearance and thus not desirable in the pediatric age group due to radiation exposure. With its wide availability, lipase is an attractive marker to identify severe cases of AP (25), but may identify many false positives because of its low positive predictive value and specificity. Coffey et al, found that serum lipase seven fold above the upper limit of normal within 24 hours of presentation helped predict acute pancreatitis severity (25). However, this is a retrospective study evaluating 211 children and has not been validated in larger study groups. Suzuki et al, in Japan, developed a pediatric-friendly severity scoring system using 9 parameters (29), but this was also a retrospective study that only evaluated 145 patients, and the authors concluded that results might not be broadly applicable to the pediatric population. More recently, Szabo et al, reported that an early severity prognostic model using serum albumin, lipase, and white blood cell count obtained within 24 hours demonstrated a positive predictive value of 35% and negative predictive value of 91% (30).

Further prospective studies are necessary to determine the clinical utility of any of these tools. The above-mentioned studies utilized various definitions of severity of AP, limiting the capacity to make comparisons across studies. A recent publication by the NASPGHAN Pancreas Committee addressed the need to have a well-defined classification of severity of AP by proposing definitions for mild, moderately severe, and severe AP to improve homogeneity among studies(31).

Serum Biomarkers—Acute pancreatitis is primarily a clinical diagnosis that relies on the presence of at least two of three criteria as published by the INSPPIRE and the Atlanta classification (8, 9). Without two of these three criteria fulfilled, it is difficult to make the diagnosis of AP. The main biochemical markers used to diagnose AP include serum lipase and serum amylase. As a serum lipase or amylase level of at least three times the upper limit of normal is considered consistent with pancreatitis, it is important to know a laboratory's reference values to determine this threshold. Both amylase and lipase are usually elevated early in the disease course. However, correlation of serum lipase or amylase levels and severity of disease is poor (25, 32, 33). Lipase is primarily secreted from the pancreas, although other sources of lipase include gastric and lingual lipases. In AP, lipase is usually increased within 6 hours of symptoms; serum levels peak at 24–30 hours and can remain elevated for more than one week (34). Some advocate that serum lipase without serum amylase is sufficient to diagnose AP, as lipase is a more sensitive and specific marker of AP (87–100% and 95–100%, respectively) (35–38). Lipase, in addition, stays elevated longer than amylase, which is useful in cases of delayed presentation (34, 39, 40). Lipase levels are also less altered by etiology of AP in contrast to amylase especially in the case of ethanol (37, 41) or hyperlipidemia (42, 43). But caution in interpreting levels in children must be exercised, as normal lipase values have been demonstrated to relate to the age of a child, rising from newborn to child to adult (44, 45). Amylase is secreted from several organs, primarily the salivary glands and the pancreas. Most laboratories measure total amylase levels which contain both s-amylase (salivary) and p-amylase (pancreas) isoforms (46). Laboratory tests exist to fractionate p- and s-amylase, but this practice is less available. Amylase reference values are different depending on the laboratory test used, but also vary with age and gender (47, 48). Serum amylase levels can be altered by the etiology of pancreatitis as noted above. Amylase levels rise faster than lipase levels and often can normalize by 24 hours after onset of symptoms limiting usefulness in patients with a delayed presentation to a medical facility (34). As the kidneys excrete amylase and lipase, non-pancreatic-based elevations of these enzymes may be seen in patients with renal injury or disease (46).

Several non-pancreatitis conditions cause elevations of pancreatic serum amylase and/or lipase, including decompensated liver failure, renal failure, intestinal inflammation (including celiac disease and inflammatory bowel disease), abdominal trauma, diabetic ketoacidosis, and head trauma (49). Additionally, some individuals produce large complexes of amylase or lipase with immunoglobulins (termed macroamylase and macrolipase) that are poorly filtered and excreted due to the large size, that will lead to elevated values if the enzyme level is measured in blood, despite not being related to inflammation of the pancreas(50).

Other biomarkers for diagnosis and management of pancreatitis have been proposed and studied in animal models or small clinical trials (reviewed in (46, 51, 52)). However, none has gained prominence and many have yet to be validated for general clinical use.

Several laboratory tests are helpful for monitoring the course of AP (53). In general, serum electrolytes, blood urea nitrogen (BUN) and creatinine and a complete blood count (CBC) are important to monitor fluid/hydration status and renal function. A hepatic enzyme panel is indicated to seek biliary or gallstone etiology and to assess for organ involvement. Calcium and triglyceride levels should be considered baseline investigations (9). Monitoring respiratory status can alert the clinician to the progression from mild to moderately severe or severe AP.

Etiologies—As mentioned previously, anatomic, obstructive (including biliary), infectious, trauma, toxic, metabolic, systemic illness, inborn errors of metabolism, genetic predispositions, and idiopathic have all been described as potential etiologies in pediatric AP, acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) (3, 4, 54). The review by Lowe et al summarized the top 6 overall etiological categories in published reviews as being idiopathic/other in 24%, trauma in 17%, systemic illness in 15%, structural abnormalities in 14%, drugs in 10%, and infections in 8%. (3) Considering more common etiologies as well as those for which directed therapies exist, a 2012 manuscript by Morinville et al presented a survey of pediatric gastroenterologists providing pancreatology care and proposed the following workup in first cases of pancreatitis: serum liver enzymes, triglyceride and calcium levels, and abdominal ultrasound. They suggested reserving testing for genetic causes/predispositions (which at the time consisted of CFTR(cystic fibrosis transmembrane conductance regulator), SPINK1 (serine protease inhibitor Kazal type 1) and PRSS1 (cationic trypsinogen)), sweat chloride, and more detailed imaging for cases of ARP, CP, or first instances of AP with increased concern for underlying risk for recurrence based on presentation, past medical history, or family history(9). As appropriate, a search can be conducted for particular toxic-metabolic risk factors(55). A recent publication by Garipey et al focused on the causal evaluation of ARP and CP in children, which tends to be more expansive due to the recurrent/chronic nature of the presentation (56) Autoimmune pancreatitis (AIP) types 1 and 2 are rarely diagnosed but represent distinct types of pancreatitis with specific histological findings in the context of suggestive symptoms, imaging, laboratory results, and response to therapy. Should AIP be suspected as the etiology of AP, further supportive evaluation is necessary. Interested readers are directed to a recent publication on pediatric AIP by Scheers et al (57).

Imaging—Imaging in the early phase of AP usually is not required if history/presenting symptoms and biochemical serum markers are present to make a diagnosis. Imaging becomes relevant to document pancreatic necrosis, complications of pancreatitis including fluid collections, and etiology or pancreatitis such as gallstones/biliary disease or anatomic abnormalities.

The gold standard for diagnostic imaging remains the CECT and several scoring systems have been developed (58). However, despite CETC being the imaging gold standard, it is frequently not indicated nor necessary for the diagnosis or management of pediatric AP. In

cases that are ambiguous for a diagnosis of AP, such as in a delayed presentation when serum markers may be low, a contrast enhanced computed tomography (CECT) might be required to confirm AP. IV contrast is key to distinguish necrotic areas in the pancreas (59). Since early imaging may underestimate extent of disease and because complications evolve over time and findings may not be present in the early phase of the disease, CECT ideally should be delayed at least 96 hours after onset of symptoms (8, 60). In mild cases, CECT may show homogenous organ enhancement, inflammatory changes of peripancreatic fat or fluid surrounding the pancreas (59). In severe cases, CECT may show heterogeneous organ enhancement, necrosis within the pancreas or in the surrounding peripancreatic tissue. In addition, CECT can also identify peripancreatic fluid collections or pseudocysts. CECT should be reconsidered when the patient's clinical condition deteriorates or is persistently severe (8). Lautz et al. found that the computed tomography severity index (CTSI or Balthazar score) in pediatric patients gave a sensitivity, specificity, positive predictive value, and negative predictive value of 81%, 76%, 62%, and 90%, respectively, for severity, in a retrospective study evaluating 64 children (61).

Ultrasound is used extensively in cases when there is a high suspicion of biliary pancreatitis, where it is useful early to determine the need for therapeutic intervention (33, 58). Ultrasound has an excellent safety profile, is non-invasive and does not utilize radiation. However, ultrasound utility can be limited in the assessment of the pancreas due to interfering structures, such as the bowel gas in the intestine and obesity, and has a lower sensitivity in visualizing the pancreas compared to CECT.

Magnetic resonance imaging (MRI) is typically not utilized as initial imaging technique in AP but can be useful for late complications (59). It can be particularly useful in young or pregnant patients (intent to limit radiation), and can allow alternative IV contrast methods in patients with impaired renal function or allergies to iodinated contrast (60). MRI may also be more sensitive in evaluating necrotic tissue as compared to CECT (59, 61). MR cholangiopancreatography (MRCP) in AP is most often employed in detecting distal common bile duct stones and diagnosing biliary causes of AP. MRI/MRCP using secretin is helpful in examining the ductular system in the pancreas as well as common bile duct abnormalities including strictures or stones (62, 63). To optimize detection of ductal abnormalities, MRCP may be performed after an attack of AP has resolved as acute edema may obscure the visualization of the ducts. The use of secretin enhanced MRCP in pediatric pancreatic disease has not been fully established (64) and access to secretin is not uniform across institutions and countries. Lin et al detail the use of MRI and MRCP in children requiring pancreatic imaging as well as overall imaging considerations in AP (65).

Summary and Recommendations—Recommendation 1a: Diagnosis of pediatric acute pancreatitis should be as per previously-published INSPPIRE criteria.

Diagnosis of AP in pediatric patients requires at least 2 of the following: (1) abdominal pain compatible with AP, (2) serum amylase and/or lipase values 3 times upper limits of normal, (3) imaging findings consistent with AP.

24/24 = 100% agreement with recommendation.

Voting results: Strongly agree = 22; agree = 2; neutral = 0; disagree = 0; strongly disagree = 0.

Recommendation 1b: Initial imaging may be accomplished via transabdominal ultrasonography, with other imaging (CT, MRI) reserved for more complicated cases +/- tailored to suspected etiology.

24/24 = 100% agreement with recommendation.

Voting results: Strongly agree = 20; agree = 4; neutral = 0; disagree = 0; strongly disagree = 0.

Recommendation 1c: Based on most frequent etiologies and those for which therapeutic options exist, first time attack of acute pancreatitis testing should include liver enzymes (ALT, AST, GGT, ALP, bilirubin), triglyceride level, and calcium level.

23/24 = 96% agreement with recommendation.

Voting results: Strongly agree = 20; agree = 3; neutral = 1; disagree = 0; strongly disagree = 0.

2. MANAGEMENT CONSIDERATIONS IN PEDIATRIC ACUTE PANCREATITIS

2a. Fluid Management in Acute Pancreatitis—Intravenous (IV) fluid therapy is a mainstay of treatment during an episode of AP. Fluid resuscitation maintains adequate fluid status and urine output, but recently attention has focused on the use of IV fluids to prevent potential complications in AP, such as necrosis and organ failure. The pathogenesis of AP and progression to severe forms is thought to be secondary to alteration in the microcirculation of the pancreas by events including hypovolemia, increased capillary permeability and formation of microthrombi. Fluid resuscitation is thought not only to correct hypovolemia but to help preserve pancreatic microcirculation by providing adequate perfusion and preventing possible microthrombi formation and thus preventing complications and progression to severe disease (66).

Type of Fluid: Consensus is lacking regarding the ideal amount and type of fluid to use during an episode of AP in adult practice, and even less data exist pertaining to fluids in the pediatric population. Crystalloid has been the most recommended type of fluid in adult guidelines (33, 67–70). A major benefit of crystalloid is that it is readily and quickly available. Normal saline (NS) has long been the crystalloid of choice for initial fluid resuscitation in general but some adult literature suggests Lactated Ringers (LR) as more optimal in AP. In a small randomized control trial (RCT) of 40 adults with AP, Wu et al showed that LR decreased the incidence of the systemic inflammatory response syndrome (SIRS) and C-reactive protein levels at 24 hours compared with NS (71). By contrast, a retrospective review of 103 patients failed to show any significant difference between LR and NS as the initial resuscitation fluid in adults with varying severities of pancreatitis (72). LR has been recommended over NS in the International Association of Pancreatology/American Pancreatic Association (IAP/APA) guidelines, but the American Gastroenterology Association (AGA) guidelines only state that LR may be a better choice but was not a strong recommendation (68, 70). In pediatrics, it has been shown that aggressive fluid management

within the first 24 hours with normal saline with dextrose 5% is a safe and well-tolerated option (73), but this was not compared to other types of IV fluids (such as LR).

Colloids (such as albumin, fresh frozen plasma, or packed red blood cells) have not been recommended as the initial resuscitation fluid in AP. Colloid components stay within the intravascular space because of larger size and can draw fluid into the circulation from the interstitium secondary to osmotic effect. The guidelines from the AGA recommend colloid in specific situations when the hematocrit is < 25% or albumin is < 2 g/dL (68), with another publication recommending a ratio of 3:1 of crystalloid to colloid (74).

Rate of Fluid Administration: The aggressiveness of fluid resuscitation in AP has also been debated. The timing of intervention of aggressive fluid therapy may be key. Adult studies in favor of early and aggressive fluids in AP include several retrospective studies that utilized different strategies such as providing > versus < 33% of total fluids within the first 24 hours, and another providing 3.5L versus 2.4L IV within the first 24 hours (75). In general, those receiving more aggressive IV fluid volumes within the first 24 hours tend to have improved outcomes including mortality, but even within the various studies, findings are inconsistent as to whether higher early IV fluids reduced rates of necrosis, systemic inflammatory response syndrome (SIRS), and length of stay (76). In contrast, Mao et al, reported a RCT of 76 patients with severe AP assigned to slow hemodilution (5–10ml/kg/h) or rapid hemodilution (10–15ml/kg/h) demonstrating that rapid aggressive early fluid administration yielded higher sepsis rates and mortality (77). de-Madaria et al conducted a prospective study of 247 patients dividing patients based on the amount of fluid administered in the first 24 hours. The group receiving the highest volume, >4.1L, had an increased rate of persistent organ failure (78). Weitz, et al, reviewed 391 cases of AP and found the use of aggressive fluids (approximately 5L) was associated with increased severity of disease and local complications (79). Concerns about this latter group of studies are that they have primarily involved sicker patients and fluid regimens were not restricted to the first 24 hours of resuscitation.

Several experts and groups have since made recommendations for the rate of fluid resuscitation in the first 24–48 hours in adults with AP. The IAP/APA guidelines recommend that patients receive 5–10 ml/kg/hr until resuscitation goals are achieved with regards to improvements in heart rate, urine output, mean arterial pressure and/or hematocrit (70). The American College of Gastroenterology (ACG) recommends an initial rate of 250–500ml/hr, in addition to boluses of fluid if hypotension or tachycardia is present, and using BUN to direct therapy (33). Similar recommendations are made in a review by Whitcomb et al (80). Aggarwal et al. advises 3–4L of fluid in the first 24 hours (not to exceed 4L) with an initial 1L bolus and to follow with 3 ml/kg/hr for the first 24–48 hours (81). Nasr et al. recommend 1–2L boluses initially and 150–300 ml/hr to follow (82). Subsequently, they recommend 2 ml/kg/hr if the patient responds to the initial resuscitation but otherwise to use 3 ml/kg/hr (82).

Only one pediatric study evaluated different rates of maintenance fluid administration, involving 201 patients with AP [69]. This study showed that a combination of early enteral nutrition (< 48 hours) and aggressive fluids (>1.5–2x maintenance in the first 24 hours)

decreased length of stay and the occurrence of severe disease versus more conventional historical management. Aggressive IV fluids did not adversely affect outcomes (primarily pulmonary complications or readmission rates). No studies specify the ideal rate of maintenance fluids in AP following the initial resuscitation (>24–48 hours), although Szabo et al, suggested that 1.5–2x maintenance was safe in their patient population (73). No pediatric studies compare initial resuscitation volumes.

Summary: In the initial resuscitation phase of acute pancreatitis, theoretical and potential clinical advantages favor LR above NS based on adult data, but pediatric data are lacking.

Recommendation 2ai: Children with acute pancreatitis should be initially resuscitated with crystalloids, either with LR or NS in the acute setting. Based on assessment of hydration status/hemodynamic status, if evidence of hemodynamic compromise, a bolus of 10–20mL/kg is recommended.

24/24 = 100% agreement with recommendation.

Voting results: Strongly agree = 22; agree = 2; neutral = 0; disagree = 0; strongly disagree = 0.

Summary: Pediatric literature is sparse regarding fluid resuscitation and rate of fluid administration in acute pancreatitis. The adult literature suggests boluses of 250mL–1000mL initially, and up to 3–4L fluids within first 24h.

Recommendation 2aii: Children with diagnosis of acute pancreatitis should be provided 1.5–2x maintenance IV fluids with monitoring of urine output over the next 24–48h.

22/24 = 92% agreement with recommendation.

Voting results: Strongly agree = 12; agree = 10; neutral = 2; disagree = 0; strongly disagree = 0.

2b. Monitoring of children diagnosed with AP/extra-pancreatic manifestations of acute pancreatitis—Although not well studied in pediatric patients, multi-organ disease in adult patients with AP is associated with worse clinical outcomes with over half of AP-related deaths occurring within 1 week of the onset of multi-organ dysfunction (83). Cardiac, pulmonary and renal involvement comprise key components of adult scoring systems used to predict severity of an AP episode including the modified Atlanta Classification, Ranson’s criteria, Japanese Severity Assessment, Glasgow Score, BISAP, and APACHE II (8, 84–87). Pediatric models predicting severity of AP have also placed importance on multi-organ involvement but have proven to be less reliable (88) or have not yet been prospectively validated (29). Increased endothelial barrier permeability and profound cytokine release associated with SIRS combined with aggressive hydration theoretically increases a patient’s risk for third-spacing fluids and developing extra-pancreatic manifestations of AP. Appropriate monitoring is vital to balance appropriate fluid resuscitation while attempting to prevent cardiac, pulmonary and renal complications (89).

Cardiovascular Monitoring: Hypovolemia at admission is a strong predictor of morbidity and mortality among adults with AP and appears to be correlated with the magnitude of the SIRS (89). Tachycardia has been utilized in both adult and pediatric scoring systems to predict severity of AP, and its improvement has been utilized to confirm adequate fluid resuscitation in addition to monitoring urine output and skin turgor (71, 81). Routine adult cardiac monitoring for non-ICU patients includes routine vitals every 8 hours to assess cardiovascular status (71). Additionally, rare cases of cardiac tamponade and atrial fibrillation have been reported in AP and should be considered during standard cardiac workup initiated in patients with unexplained hypotension, shortness of breath and/or chest pain (90–93).

Pulmonary Monitoring: Both adult studies and animal models show acute respiratory distress syndrome (ARDS), pneumonia and pulmonary edema/effusions as early complications of AP, typically within the first 48 hours (15, 94). As ARDS is the most common critical complication of severe AP associated with multi-organ dysfunction in adults (95), abnormal P_aO_2 or abnormal pulmonary imaging are components of all commonly used scoring systems to predict severity of an AP episode (8, 29, 84–87). Routine monitoring of oxygen saturation during aggressive hydration is typically implemented, with some advocating patient beds be elevated at 30-degree angle to decrease likelihood of pulmonary sequestration (71). Standard pulmonary workup and care should be considered in any patient with unexplained shortness of breath, worsening cough and/or difficulty breathing (94).

Renal Monitoring: Acute kidney injury (AKI) via abdominal compartment syndrome (83, 96) or inflammatory-driven damage to the proximal convoluted tubule (97) marked by elevation of BUN and creatinine, along with decreased urine output, is a known early complication of AP in children and factors prominently in AP scoring systems to predict disease severity (8, 15, 29, 84–87). BUN alone in some adult studies has been shown to be as effective in predicting disease severity as more advanced scoring systems (98) and AKI has been associated with a 10-fold increased risk of mortality in severe AP (99). Therefore, BUN and creatinine are considered important markers to follow in assessing fluid management and to monitor for AKI in adults during the first 48 hours and during aggressive hydration (71, 81, 98). While no guidelines document the frequency of monitoring these parameters, 8–12 hours was used in one study to determine responsiveness to fluid management (71). Guidelines from the ACG stress the importance in decreasing the BUN and maintaining a normal creatinine within the first 24 hours so early monitoring is essential (33). In rare cases, continuous veno-venous hemofiltration (CVVH) is required to prevent further kidney damage, prevent abdominal compartment syndrome and/or remove inflammatory cytokines, but its use has not been studied in pediatric patients with AP (100). It may be necessary to install a urinary catheter to accurately document urinary output, particularly in a sedated child within the intensive care unit setting.

Summary and Recommendations: Monitoring of patients with acute pancreatitis can provide indicators of complications arising, including SIRS and organ dysfunction/failure. Cardiac, respiratory, and renal status should be followed particularly closely within the first

48h after presentation as most complications will have their onset within that time-frame. Urine output is an important marker of adequate fluid resuscitation, with adult literature suggesting benefit to aim for > 0.5–1cc/kg/hour (IAP/APA guidelines).

Recommendation 2bii: In patients admitted to an inpatient ward, vitals should be obtained at least every 4 hours during the first 48 hours of admission and during periods of aggressive hydration to monitor oxygen saturation, blood pressure and respiratory rate. Frequency to be adjusted based on clinical status. Abnormalities of vital signs should prompt specialist assessment.

22/24 = 92% agreement with recommendation.

Voting results: Strongly agree = 16; agree = 6; neutral = 1; disagree= 1; strongly disagree= 0.

Recommendation 2biii: BUN, creatinine and urine output should be monitored routinely during the first 48 hours as marker of appropriate fluid management and to screen for acute kidney injury. Abnormalities should prompt nephrology assessment.

22/24 = 92% agreement with recommendation.

Voting results: Strongly agree = 18; agree = 4; neutral = 1; disagree= 1; strongly disagree= 0.

2c. Pain Management in Acute Pancreatitis—Abdominal pain is the most common presenting symptom of AP. In pediatric AP studies, 80% to 95% of patients presented with abdominal pain. Patients present with epigastric pain in 62% to 89% and diffusely in 12% to 20%. The “classic” presentation of epigastric pain radiating to the back occurs in only 1.6% to 5.6% of pediatric patients (15, 16).

The pathophysiology of AP is characterized by a loss of intracellular and extracellular compartmentalization, which could result from different mechanisms: obstruction of pancreatic secretory transport; activation of enzymes; or inability to stop the activation cascade. AP occurs in genetically susceptible individuals in whom the inflammatory reaction causes pancreatitis. This in turn stimulates visceral pancreatic and somatic peritoneal pain receptors(101). Other postulated mechanisms causing AP pain include high pressures within the gland or pancreatic duct and subsequent gland ischemia. Pain in AP is also likely related to the release of tachykinin substance P and calcitonin-gene-related peptide. Factors which stimulate primary sensory neurons include hydrogen ions, heat, leukotrienes, arachidonic acid metabolites, bradykinins and proteases, such as trypsin, released during AP (102).

Control of pain is an important therapeutic goal in the management of AP and commonly involves use of peripherally and centrally acting analgesics. No data are published on optimal pain management in pediatric AP, and studies in adults have not identified a single superior medication (67).

Opioid Analgesics: Because classic peripherally acting analgesics (such as acetaminophen) often are insufficient in severe pancreatitis, opiates are required frequently to control pain. Morphine or related opioids were utilized by 94% of respondents to manage children with AP according to the 2012 INSPPIRE physician questionnaire (103). Morphine had been reported to cause sphincter of Oddi dysfunction after systemic administration (104). However, no clear evidence supports this theory and morphine can be used safely in patients with AP (105). Meperidine has been used in adults with AP but drawbacks include its short half-life and potential of neurotoxicity through the buildup of toxic neurometabolites that can lead to seizures, myoclonus and tremors (106). A review of narcotics and sphincter of Oddi function by Thomson et al, documents that no studies to date directly compare the effects of meperidine and morphine on sphincter of Oddi manometry and no comparative studies exist in patients with AP. Furthermore, no studies or evidence exist to indicate morphine is contraindicated for use in AP(107). A Cochrane review from 2013 includes 5 studies with a total of 227 subjects to assess the efficacy and safety of several opioids. Medications included were buprenorphine, pethidine, pentazocine, fentanyl and morphine. The overall conclusion is that opioids may be an appropriate choice in the treatment of pain related to AP and they may decrease the need for supplementary analgesia. Additionally, the risk of pancreatitis-associated complications or clinically serious adverse events is not different comparing opioids and other analgesic agents (108).

Opioid sparing analgesics: NSAIDs have been hypothesized to be potential contributors to the development of AP but have also shown benefit in AP pain management. Prophylactic NSAIDs including indomethacin and diclofenac have been shown to be useful in several studies in the prevention of post-ERCP pancreatitis (109, 110). With respect to pain management post AP diagnosis, indomethacin has been found to be superior to placebo and did not show an increased risk of GI bleeding in a small study (111). When compared to morphine, metamizole showed improved pain relief at 24 hours but the difference did not reach statistical significance (105).

Systemic administration of local anesthetics, mainly procaine, has been advocated as basic analgesia for AP. Intravenous procaine is proposed to decrease pain and/or the necessity for auxiliary analgesic medication and possibly improve the clinical course of AP. In one controlled trial, systemic administration of procaine in pancreatitis improved and accelerated postoperative recovery after major abdominal surgery, including diminished pain, improved cognitive function, and shortened duration of ileus as well as overall hospitalization(112). But evidence is limited and there is lack of placebo-controlled data.

Epidural anesthesia (EA) widely used to induce analgesia in the perioperative period and has also been used to decrease pain in patients with AP. The mode of action has been attributed to a sympathetic nerve blockade that redistributes splanchnic blood flow to non-perfused pancreatic regions. In a study of 35 patients with predicted severe AP, EA was shown to significantly decrease pain scores, improve pancreatic perfusion based on radiological perfusion studies, and improve clinical outcomes (decreased requirement for necrosectomy) (113). And, a prospective study of 121 patients demonstrated good efficacy and safety of EA in adult AP (114).

Summary: No data provide guidance for optimal pain management in pediatric AP. Studies in adults have not identified a single superior medication. No evidence exists supporting the contention that morphine causes adverse events on the sphincter of Oddi.

Recommendations 2ci: Intravenous morphine or other opioid should be used for acute pancreatitis pain not responding to acetaminophen or NSAIDs.

24/24 = 100% agreement with recommendation.

Voting results: Strongly agree = 18; agree = 6; neutral = 0; disagree = 0; strongly disagree = 0.

Recommendation 2cii: Acute pain specialist services should ideally be consulted in cases of more severe pain to optimize pain management.

23/24 = 96% agreement with recommendation.

Voting results: Strongly agree = 18; agree = 5; neutral = 1; disagree = 0; strongly disagree = 0.

2d. Enteral and Parenteral Nutrition in Pediatric Acute Pancreatitis

Oral and Enteral Nutrition: Traditionally, AP patients were managed by keeping nil per os (115) and giving parenteral nutrition (PN) (116). It was hypothesized that by resting the gut, the pancreas was allowed to “rest” and thus heal more rapidly. The rationale behind this theory was that presence of food in the intestines would stimulate cholecystokinin (CCK) release, which in turn would stimulate pancreatic enzyme secretion, which could lead to further activation of proteolytic enzymes and exaggerate the autodigestion process and worsen the injury (117, 118)

In adults, a number of controlled studies, reviews and meta-analyses pertain to nutritional therapy in both severe and mild AP, including a review by the Dutch Pancreatitis Study Group and consensus guidelines published by the *International Consensus Guideline Committee* (119). Lodewijkx et al, support enteral nutrition as being superior to parenteral nutrition, and an on-demand feeding strategy in predicted severe AP (120). Mirtallo et al reviewed 8 societal reports in order to develop international consensus guidelines for nutrition therapy in AP (119). They concluded that in adult AP, enteral nutrition (EN) was preferable to PN and should be used first even in the presence of fistulas, ascites and pseudocysts.

The timing of EN initiation has been advocated to be as early as possible, especially as one of the goals of EN is to prevent bacterial translocation and thereby prevent the development of SIRS. Early nutritional therapy is also purported to decrease cytokine response and incidence of gastroparesis and intestinal ileus. While some studies (121) show no difference in outcomes when EN was initiated before or after 72 hours of presentation, a 2008 meta-analysis examining eleven RCTs demonstrated that EN started within 48 hours of presentation significantly decreased rates of mortality, infections and multiorgan failure compared with PN (122). These effects were diminished when EN was started after 48

hours. In a 2011 review of nutritional support of adult AP, it was concluded that *early* nutritional support, particularly EN, but also PN, reduced complications and improved survival (123). This review stated that to be effective, nutritional support had to begin within 72 hours. It has been stated that EN should be considered “*an active therapeutic intervention that improves the outcome of patients with pancreatitis*” (124).

Clinical studies comparing the outcomes of PN and EN in patients with AP report that the use of EN in Severe Acute Pancreatitis (SAP) or predicted SAP results in significantly lower rates of complications (125–133). A recent meta-analysis demonstrated superiority of EN compared with PN with a lower incidence of infection and multiorgan failure, resulting in lower mortality rates and a shorter hospital stay (134). However, since full EN may not always be feasible during AP because of increase in pain or feeding intolerance, some have advocated a role for a combination of EN and PN. In one study that randomized 100 patients to receive PN alone vs PN in combination of EN or EN alone, sepsis, intra-abdominal infection, and length of hospitalization declined when EN was included in the management (135).

The routes of EN described have included gastric and jejunal. Two small studies found no difference in outcomes between nasogastric (NG) and nasojejunal (NJ) fed groups (136, 137). A meta-analysis of 10 RCT showed no differences in outcomes between groups receiving (semi)elemental and polymeric formulas. (138)

No guidelines have been published relating to nutritional support of children with AP. A recent study by Abu-El-Haija et al. demonstrated the feasibility of establishing enteral feeds in pediatric AP, without complicating the course or affecting the pain scores of AP (139). From the same center, a retrospective study showed that a combination of early enteral feeds plus greater than 1.5 times maintenance IV fluids were associated with a shorter length of stay and milder illness compared with those who remained NPO for 48 hours and had lower rates of IVF than 1.5 times maintenance (73). Two children with severe AP are reported who were treated successfully with nasojejunal feedings in a PICU and switched to oral feeding when discharged to the general ward (140).

Parenteral Nutrition: Parental nutrition provides the required calories and nutrients to compensate for a catabolic state. Concern that PN could further stimulate the pancreas and result in exaggeration of the autodigestive process has not been supported by the literature (141, 142). Data indicates that infusion of protein does not stimulate pancreatic secretions (143). When comparing different PN formulations, PN enhanced with glutamine has been reported to reduce overall complication rates, as well as reduce length of stay (LOS) (144–148). The administration of IV glucose also does not appear to stimulate pancreas secretion (149, 150). Infusion of glucose in critically ill patients may be useful to provide an easily accessible energy source during a catabolic state and counteract gluconeogenesis from protein breakdown. But glucose infusion must be monitored, as it may predispose to hyperglycemia (151), as an inflamed pancreas may not mount an appropriate insulin response.

Hypertriglyceridemia is associated with severe AP (152–155), but the mechanism leading to SAP is not clear (156). Insufficient data exist to recommend or to discourage the use of parenteral lipids in AP.

With respect to the timing of PN in AP, where the measured outcome was mortality, data suggest that early PN is significantly more beneficial than bowel rest in adult severe AP (122). In all cases where EN is not possible for a prolonged time, such as in ileus, complex fistulae, and abdominal compartment syndrome, PN has been advocated. In contrast, a recent study advocated for delaying initiation of PN to 7 days in critically ill children due to increased risk of infection, and increased complication rates when PN was initiated within the first 24 hours of ICU stay. Early enteral nutrition was allowed in both groups. However, the presence or percentage of AP patients specifically was not specified in that report (157).

Summary: Adult literature supports early enteral nutrition to reduce AP complications and improving survival. Pediatric literature supports early enteral nutrition in mild AP cases, and small case report in severe AP.

Recommendation 2di: Except in the presence of direct contraindications to use the gut, children with mild acute pancreatitis may benefit from early (within 48–72h of presentation) oral/enteral nutrition to decrease length of stay and decrease risk of organ dysfunction.

22/24 = 92% agreement with recommendation.

Voting results: Strongly agree = 17; agree = 5; neutral = 1; disagree = 0; strongly disagree = 1.

Recommendation 2dii: Parenteral nutrition (PN) should be considered in cases where EN is not possible for a prolonged period of time (longer than 5–7 days) such as in ileus, complex fistulae, abdominal compartment syndrome, to reduce the catabolic state of the body. Enteral nutrition should commence as soon as feasible, with a combination of EN and PN being superior to sole PN.

22/24 = 92% agreement with recommendation.

Voting results: Strongly agree = 15; agree = 7; neutral = 1; disagree = 0; strongly disagree = 1.

Recommendation 2diii: In cases of pancreatic laceration, fracture, or duct disruption, it is unclear whether oral/enteral feedings may be detrimental in the acute phase. This must be further studied.

21/24 = 88% agreement with recommendation.

Voting results: Strongly agree = 13; agree = 8; neutral = 2; disagree = 0; strongly disagree = 0; no vote = 1.

2e. Use of Antibiotics in Pediatric Acute Pancreatitis—The rationale for consideration of antibiotics in the management of AP relates to the concern for bacterial

infection from translocated intestinal microbiota. Antibiotics are not recommended for use in adult mild AP (70).

In the management of adult severe AP, antibiotics have been studied to prevent and manage infections. Imipenem and/or third generation cephalosporins have been most often used historically in an attempt to reduce morbidity and mortality. This prophylactic approach is controversial, with prior studies suggesting benefit (158–160), while other studies did not demonstrate benefit from routine use (161) in the absence of documented infection. Prophylactic antibiotics have been used in the setting of sterile necrotizing pancreatitis to prevent infected necrotizing pancreatitis (162, 163), particularly imipenem (163). However, systematic reviews do not support a benefit regarding mortality, for infections not involving the pancreas, or for the reduction of surgical interventions in adults (162). More recent meta-analyses support the use of antibiotics for *infected* necrotizing pancreatitis but not for *sterile* necrosis (164–166). Current adult AP recommendations are to use antibiotics only for infected necrosis, or in patients with necrotizing pancreatitis who are hospitalized and not improving clinically without antibiotic use (70). Infected necrosis should be suspected if the patient's clinical status is worsening with fevers, or with presence of gas within collections on imaging. In certain situations aspiration of the fluid by an endoscopic-guided technique or via interventional radiology and establishment of appropriate drainage may be needed to guide management(8). For necrotizing pancreatitis, antibiotics known to penetrate necrotic tissue are recommended, such as carbapenems, quinolones, and metronidazole, as antibiotic use in this setting has been demonstrated to delay surgical interventions and decrease morbidity and mortality (33).

Documented infections originating outside the pancreas should be treated as indicated.

No studies have been published on the use of antibiotics in the management of AP in children.

Summary: Antibiotics should not be used in the management of AP, except in the presence of documented infected necrosis, or in patients with necrotizing pancreatitis who are hospitalized and not improving clinically without antibiotic use. Antibiotics known to penetrate necrotic tissue should be used in management of infected pancreatic necrosis as these may delay surgical intervention and decrease morbidity and mortality.

Recommendations 2ei: Prophylactic antibiotics are not empirically recommended in severe acute pancreatitis.

23/24 = 96% agreement with recommendation.

Voting results: Strongly agree = 20; agree = 3; neutral = 1; disagree= 0; strongly disagree= 0.

Recommendation 2eii: Antibiotic use is indicated only in cases of documented infected necrosis in acute pancreatitis.

16/24 = 67% agreement with recommendation. Recommendation not supported. This was identified as an area of particular controversy requiring further study.

Voting results: Strongly agree = 10; agree = 6; neutral = 2; disagree= 4; strongly disagree= 0; no vote = 2.

2f. Use of Protease inhibitors in Pediatric Acute Pancreatitis—As AP is hypothesized to be a necroinflammatory process begun through the acute, and inappropriate, activation of the protease trypsin and pancreatic zymogens within the parenchyma, investigators have been keenly interested in blocking this inflammatory process to limit extent of injury.

The two main compounds described in the literature to inhibit this enzyme activation include the serine protease inhibitor gabexate mesilate and the trypsin inhibitor aprotinin. In 1993, Pederzoli et al. reported results of a randomized, double-blind multicenter clinical trial on use of gabexate mesilate versus aprotinin in AP therapy. In this study, gabexate mesilate appeared more favourable to aprotinin for the period 24–72 hours, but importantly, a placebo control arm is missing (167). Timing of treatment and mode of delivery seem to be key factors in efficacy (167, 168). Ino et al. studied the efficacy of continuous regional artery infusion CRAI with gabexate mesilate and antibiotics for severe AP via a small prospective study involving 9 patients receiving CRAI for 3–5 days and 9 others receiving systemic protease inhibitor therapy and antibiotics. Abdominal pain and SIRS disappeared quicker, LOS was significantly shorter in the CRAI group (168). CRAI of anti-proteases and antibiotics has been reported to reduce CRP and APACHE II scores when initiated within 72 hours of onset of illness (169), an approach described in pediatric patients as well (170).

A 2007 review by Kitagawa and Hayakawa found no evidence to justify the routine use of anti-proteases in AP, and although the use of continuous intravenous high-dose protease inhibitors and antibiotics might be effective in preventing the exacerbation of severe AP, cost-effectiveness studies were necessary. Of importance, these compounds are not Food and Drug Administration (FDA)- approved in the United States (171–173).

Summary: Certain adult studies support use of anti-proteases in the management of severe AP, but no definite recommendations have ever been made for their use. Studies are not randomized with placebo controls and only a few cases are described in pediatric patients.

Recommendations 2f: Anti-proteases cannot be recommended in the management of acute pancreatitis in children at this time.

24/24 = 100% agreement with recommendation.

Voting results: Strongly agree = 17; agree = 7; neutral = 0; disagree= 0; strongly disagree= 0.

2g. Use of Antioxidants in Pediatric Acute Pancreatitis—Oxidative stress contributes to injury in AP, through formation of oxygen free radicals that cause damage to the lipid pancreatic cell membrane, depolarization of the mitochondrial membrane, and induction of DNA fragmentation (174). This contributes to edema, generation of pain and may also be involved with the process of necrosis. Antioxidants have thus been hypothesized

to be of potential benefit as adjunct management in AP by preventing the formation of free radicals or scavenging existing oxygen free radicals.

The agents most studied have been antioxidant vitamins (ascorbic acid, α tocopherol, β -carotene), inorganic antioxidants (selenium) and glutamine. Two partially-overlapping meta-analyses published in 2015 utilize different methodologies to assess benefit of antioxidants in acute pancreatitis, one reviewing 11 and other 12 adult randomized controlled trials [169, 170]. Pederzoli et al, found that antioxidants reduce the number of AP complications and shortened LOS, with glutamine reducing complications and mortality rates [169]. Ino et al, reported that antioxidant therapy shortens LOS, and decreases serum CRP, but only after 10 days [170].

A significant limitation of published data of antioxidants in adult AP is that trials have included the entire spectrum of mild to severe AP. Additionally, different combinations of antioxidants and timing of delivery have been utilized in trials. Large randomized studies lack standardization of specific antioxidants as well as timing and duration of treatment.

No data exist on antioxidant use in AP in the pediatric population.

Summary: Pediatric data regarding the use of antioxidants in AP is lacking Adult publications display significant heterogeneity with respect to composition, timing, and duration of therapy. Despite potential benefits described in the adult series, evidence is insufficient to support their use in pediatrics at this time.

Recommendation 2g: Antioxidants should not be considered standard therapy in the management of pediatric acute pancreatitis.

22/24 = 92% agreement with recommendation.

Voting results: Strongly agree = 15; agree = 7; neutral = 1; disagree= 0; strongly disagree= 1.

2h. Role of Probiotics in Pediatric Acute Pancreatitis—Up to third of adult patients may develop severe AP, characterized by SIRS, organ failure and an increased risk of infection(175). In patients with infected peri-pancreatic and pancreatic necrosis, the risk of mortality is significantly increased. Reduction of gut permeability and bacterial overgrowth during AP is hypothesized to decrease the risk of infected pancreatic necrosis and thereby decrease the risk of mortality (176, 177).

The World Health Organization defines probiotics as “live microbes which, when administered in adequate amounts, confer a health benefit to their host”. Probiotics have been shown to play a role in maintaining gut microflora balance, inhibiting the growth of harmful bacteria, and enhancing immune function(178). Of importance, published studies have utilized different compositions and dosing regimens of probiotic bacteria.

Muftuoglu et al. demonstrated that *lactobacillus acidophilus* and *bifidobacterium lactis* decrease the severity of histological damage in an experimental pancreatitis model (178). Early small adult clinic trials suggested a beneficial role for probiotics in the management of

AP. Olah et al. randomized 45 patients to receive either 10^9 live or heat killed *Lactobacillus plantarum* twice daily together with enteral feeds (179). They found a statistically significant lower risk of infected pancreatic necrosis in the study group compared with control groups.

However, subsequently, the PROPATRIA study, a double-blinded, placebo-controlled randomized, multicenter study on the role of probiotics in preventing infectious complications in AP) consisting of 298 adult patients with predicted severe AP, demonstrated a significantly higher risk of mortality in the multispecies probiotic group (180, 181). Two small randomized trials since completed did not demonstrate an increase in mortality (182, 183), but the impact of the adverse findings of the PROPATRIA study has led to generalized caution in use of probiotics in adult AP.

No pediatric study has examined the role of probiotics in children with AP.

Summary: Subsequent to small case series suggesting a potential benefit of probiotics in adult AP, a large randomized study demonstrated increased mortality in a probiotic group. No pediatric studies have been published.

Recommendations 2h: Probiotics cannot be recommended in the management of pediatric acute pancreatitis at this time. Highest-quality published adult evidence suggests they may not only be of no benefit, but increase mortality.

23/24 = 96% agreement with recommendation.

Voting results: Strongly agree = 14; agree = 9; neutral = 1; disagree = 0; strongly disagree = 0.

2i. Role of Endoscopy in Pediatric Acute Pancreatitis—Various causes of duodenal mucosal inflammation have been linked to increased risk of AP. Celiac disease pancreatic-associated manifestations include endocrine and exocrine insufficiency, acute and chronic pancreatitis, malnutrition, papillary stenosis secondary to duodenitis, or immunological disturbances and have all been hypothesized to be implicated mechanistically (184–186). Gallstone disease has been found in up to 34% of Crohn's patients and may manifest as AP (187). Autoimmune pancreatitis (AIP) and primary sclerosing cholangitis (188) can also be found in patients with inflammatory bowel disease presenting with AP (189–191). While IgG4 elevation is seen in Type I AIP in adult patients, pediatric patients with AIP present commonly without IgG4 elevation, where biopsies from the duodenum or gastro-duodenal inflammatory lesions can be helpful in the diagnosis (192, 193). Acute and chronic pancreatitis have been uncommonly reported as manifestations or associations of *H. pylori* infection (194, 195). Exceedingly rare though possible causes of pancreatitis in children are tumors involving the ampulla or peri-ampullary region of the duodenum. Such lesions may be first identified by radiographic imaging, but can also be found at the time of endoscopic assessment. From available case reports, the mechanism by which these patients develop recurrent pancreatitis is not fully understood, but is likely related to tumor obstruction at the level of the ampulla (196, 197). But in general, the role of esophagogastroduodenoscopy in AP is limited.

No studies evaluate indications or benefits of esophagogastroduodenoscopy in pediatric AP.

Summary: The role of endoscopy in the acute care of children with AP is unclear. The potential for primary extra-pancreatic diseases resulting in the development of AP requires thoughtful consideration.

Recommendations 2i: Esophagogastroduodenoscopy is not considered a standard diagnostic tool in pediatric acute pancreatitis at this time. Indication for its use should be determined on a case-by-case basis.

24/24= 100% agreement with recommendation.

Voting results: Strongly agree = 18; agree = 6; neutral = 0; disagree= 0; strongly disagree= 0.

2j. Role of ERCP in Pediatric Acute Pancreatitis—The role for ERCP in AP has evolved with technological improvements in the diagnostic capabilities of MRI/MRCP and with increasing pediatric experience with endoscopic ultrasound (EUS). With the availability of these latter diagnostic tools for pancreatic disorders, ERCP is increasingly being used primarily for therapeutic interventions or for unclear diagnoses following MRCP or EUS. ERCP is safe in children with the most common complication being mild post-ERCP pancreatitis, occurring at rates similar to those in adults (~3–10%) when being done by experienced endoscopists (198–206). Biliary obstruction and chronic pancreatitis are the most common indications for ERCP in children. In pediatric AP, ERCP has a limited role, performed almost exclusively for biliary pancreatitis secondary to choledocholithiasis or sludge. ERCP for choledocholithiasis without pancreatitis is safe and effective (207, 208), but no specific recommendations exist in pediatrics about the timing of ERCP in choledocholithiasis or acute biliary pancreatitis. In adults, a large meta-analysis and the IAP evidence-based guidelines for management of acute biliary pancreatitis have recommended ERCP within 48 hours of symptomatic onset if patient has obstructive jaundice and/or cholangitis. Otherwise, ERCP can be done electively for uncomplicated choledocholithiasis and in other cases of biliary pancreatitis, regardless of severity (209, 210).

Less common indications for ERCP in AP are pancreatic ductal stones, strictures, pseudocyst drainage, and pancreatic duct leaks (211). Pancreatic ductal stones and strictures are typically features of acute recurrent or chronic pancreatitis, thus are relatively uncommon indications for ERCP in AP. In rare circumstances when ductal obstruction prevents resolution of pancreatitis, therapeutic ERCP can be performed. Pancreatic pseudocysts in children can occur from acute or chronic pancreatitis, but the majority occurs following blunt trauma. Pancreatic pseudocysts, are homogenous collection of pancreatic fluid enclosed by fibrous or granulation tissue but lacking an epithelial lining (15, 212), and can develop from fluid collections persisting greater than 4 weeks (213). ERCP can be used to assess communication of the pseudocyst with pancreatic duct, where a transpapillary stent can be placed for drainage. Otherwise, endoscopic cystgastrostomy (214–216) and EUS-guided drainage (217) are safe and effective ways to drain pancreatic pseudocysts in children and may be considered based on the location of the pseudocyst. Pancreatic duct injury and

leak can also occur from trauma. Early endoscopic or surgical intervention may help to minimize ongoing morbidity from a ductal leak, as ERCP provides a rapid and more definitive method to delineate the location and extent of injury than MRCP or CT and also provides the opportunity for therapeutic stent placement across the injury (218, 219).

Summary: The role of ERCP in acute pancreatitis primarily relates to therapeutic management of biliary pancreatitis secondary to choledocholithiasis or sludge. Adult literature suggests the performance of ERCP within 48 hours of symptomatic onset if patient has obstructive jaundice and/or cholangitis. Less common indications for ERCP in acute pancreatitis are pancreatic ductal stones, strictures, pseudocyst drainage, and pancreatic duct leaks or ductal lacerations.

Recommendations 2ji and 2jii: (2ji) The role of ERCP is limited in acute pancreatitis and depends on local expertise. (2jii) ERCP is indicated in management of acute pancreatitis related to choledocholithiasis causing biliary pancreatitis, and for pancreatic duct pathologies such as ductal stones or ductal leaks.

24/24 = 100% agreement with recommendation.

Voting results: Strongly agree = 21; agree = 3; neutral = 0; disagree = 0; strongly disagree = 0.

2k. Role of EUS in Pediatric Acute Pancreatitis—Endoscopic ultrasonography (EUS) has been utilized to help determine the etiology of AP. EUS not only comprehensively evaluates the pancreatic parenchyma and duct, but also the hepato-biliary anatomy. Biliary disease such as choledocholithiasis can be evaluate with EUS especially when transabdominal ultrasound does not visualize the distal common bile duct. EUS can also determine the presence of microlithiasis in the gallbladder that many times is not visualized on transabdominal ultrasound or CT scan. Microlithiasis can lead to AP, and is treatable with cholecystectomy (220). Although extremely rare in children, pancreatic tumors which could be due to pancreatic neoplasm or AIP can present with AP and be further evaluated with EUS with the possibility of pancreatic tissue sampling (221, 222).

The therapeutic role of EUS in AP is mostly limited for the treatment of complications of AP, namely pancreatic fluid collections or walled off necrosis. EUS has been shown to be useful in the management of pancreatic fluid collections/or necrosis secondary to severe AP. Spontaneous resolution of pseudocysts is believed to occur more commonly in children than adults, especially if < 5cm in size (expert opinion). Thus, most collections of any type can be managed conservatively and therapeutic intervention is not necessary in the acute setting except with evidence of infection (223). However, if maturation occurs (typically after 4–6 weeks), self-resolution is less likely, and the patient may need endoscopic drainage. Other indications for EUS intervention and drainage include large size when causing clinical symptoms, suspected infected collections or persistent symptoms from the pseudocyst. EUS-guided drainage and the creation of a cystgastrostomy has been demonstrated to be as effective and safe as surgical cystgastrostomy and has been shown to be successful even in children (224).

Summary: Based on adult literature, EUS may be useful to determine the etiology of acute pancreatitis which may include diagnosis of distal common bile duct stones, pancreatic masses, or autoimmune pancreatitis. Its role for therapy is mostly limited for the treatment of complications of acute pancreatitis, namely pancreatic fluid collections or walled off necrosis secondary to severe AP.

Recommendation 2k: EUS is not considered a standard diagnostic tool in pediatric acute pancreatitis at this time. Indication for its use should be determined on a case-by-case basis.

24/24= 100% agreement with recommendation.

Voting results: Strongly agree = 18; agree = 6; neutral = 0; disagree= 0; strongly disagree= 0.

2L Role of Surgery/Surgical Consultation in Pediatric Acute Pancreatitis—

Surgical interventions are not part of the algorithm in the management of a typical episode of AP. Publications relate to adult experience. An early indication for surgery includes management of abdominal compartment syndrome. However, management of pancreatic necrosis with early necrosectomy within first 72h has been shown to lead to increased morbidity and mortality compared to those delayed at least to beyond 12 days (225). Guidelines by the International Association of Pancreatology from 2002 suggest that delaying necrosectomy surgery for at least 3 to 4 weeks after onset of disease leads to lower morbidity and mortality(210). The 2013 ACG guidelines on the management of adult AP have commented on consideration of surgery in the context of gallstone pancreatitis, debridement of necrosis (infected vs. sterile), and minimally invasive management of pancreatic necrosis (33). Recommendations included early cholecystectomy during the same hospitalization for a mild attack of gallstone pancreatitis, and discussion between gastroenterology and surgery for timing of cholecystectomy versus other therapeutic options in cases of severe AP, especially with necrosis. For patients with persisting clinical instability and deterioration in the context of pancreatic necrosis, drainage may be necessary to improve patient status and limit morbidity and mortality. The ACG guidelines propose that debridement of necrosis should be delayed whenever possible, ideally to beyond four weeks from presentation, to allow inflammatory reactions to be better organized. Even in need of necrosectomy, less invasive methods including percutaneous radiologic, or endoscopic drainage/debridement should be considered along with laparoscopic surgical management as options to be favored above open surgery (33).

The 2015 PONCHO trial involving 266 inpatients randomized to interval cholecystectomy or same-admission cholecystectomy also supported that same-admission cholecystectomy reduced the rate of recurrent gallstone-related complications in adult patients with mild gallstone pancreatitis with very low risk of cholecystectomy-related complications (226).

In cases of severe abdominal trauma requiring emergent laparotomy (including motor vehicle accidents), injury to the pancreas should be sought, including those involving the pancreatic duct. The severity of pancreatic trauma may be graded according to the American Association for the Surgery of Trauma Pancreas Injury Scale, wherein 5 grades of injury may be assigned (227). Higher grade injuries to the pancreas from trauma typically also

include associated duodenal injuries. Those with milder blunt grade I and II injuries may be managed non-operatively. In cases of pancreatic trauma, a multidisciplinary approach involving the medical/gastroenterology and surgical teams is indicated.

The pediatric literature regarding the indications for surgery is much more limited. With regards to biliary pancreatitis, a retrospective case series of 19 children admitted with biliary pancreatitis reported 9 children undergoing early cholecystectomy with no adverse events, and 4 of 10 children that had delayed surgery experiencing adverse clinical events (including recurrence of pancreatitis) (228).

Summary: Indications for acute surgical intervention in AP indications include abdominal trauma where patient instability and/or search for associated injury to other organs is occurring. In the context of biliary pancreatitis, cholecystectomy has been shown to not only be safe but prevent recurrences if occurring within the index hospitalization. Adult literature suggests that early intervention in pancreatic necrosis leads to increased morbidity and mortality, and hence debridement of pancreatic necrosis causing patient instability should preferably be delayed at least 4 weeks from presentation and ideally performed by endoscopic or percutaneous means.

Recommendation 2li: Cholecystectomy safely can and should be performed before discharge in cases of mild uncomplicated acute biliary pancreatitis.

22/24 = 92% agreement with recommendation.

Voting results: Strongly agree = 16; agree = 6; neutral = 1; disagree= 1; strongly disagree= 0.

Recommendation 2lii: In the management of acute necrotic collections, interventions should be avoided and delayed, even for infected necrosis, as outcomes are superior with delayed (> 4 weeks) approach.

21/24= 88% agreement with recommendation.

Voting results: Strongly agree = 15; agree = 6; neutral = 2; disagree= 1; strongly disagree= 0.

Recommendation 2liii: When drainage or necrosectomy is necessary, non-surgical approaches including endoscopic (EUS, and ERCP-assisted) or percutaneous methods are preferred over open necrosectomy or open pseudocyst drainage.

24/24 = 100% agreement with recommendation.

Voting results: Strongly agree = 15; agree = 9; neutral = 0; disagree= 0; strongly disagree= 0.

3. OUTCOMES OF PEDIATRIC ACUTE PANCREATITIS

Overall outcomes in AP in children are favorable compared to adults. The average length of hospitalization for children with AP averages 2.8 to 8 days, although infants/toddlers tend to

be admitted for a longer period of time (average 19.5 days) (15, 73, 229–231). Early initiation of enteral nutrition and aggressive fluid resuscitation has been linked to shorter hospital stay, fewer intensive care unit admissions, and decreased rates of severe AP compared to patients who are kept NPO (73). These findings appear generally in line with most adult studies(232), but may not have been applied to pediatric patients until recently. Higher mortality in pediatric AP is associated with systemic disease but is low overall and is less than 5% in most cohorts, even including intensive care unit admissions (15, 30, 233, 234).

Early onset complications in AP include multi-organ dysfunction or shock (15). Acute peripancreatic fluid collections are seen in the acute phase of pancreatitis and tend to resolve spontaneously. The frequency of pseudocyst formation ranges from 8% to 41% in children with pancreatitis, and higher rates are seen in patients who present with pancreatitis related to abdominal trauma (15, 212, 235). Pseudocysts are often asymptomatic and can be managed conservatively or become larger and cause abdominal pain, vomiting, or fever. They can also become infected in 10–15% of cases (236). Another late-onset complication relates to pancreatic necrosis. Necrosis can manifest firstly as an acute necrotic collection (ANC) and then mature to walled-off necrosis (WON) (8). Management options for drainage of pseudocysts and walled-off necrotic collections include endoscopic (transpapillary or transmural) drainage, percutaneous catheter drainage, or open/laparoscopic surgery. The modality chosen depends on size, location, anatomy and the risks/benefits of the procedure, although percutaneous and endoscopic ultrasound (EUS)-guided transgastrointestinal drainage is now becoming more widely accepted (237).

Approximately 15%–35% of children with acute pancreatitis will have another bout of pancreatitis. Pediatric acute recurrent pancreatitis is associated with pancreatico-biliary anomalies, autoimmune pancreatitis, metabolic disorders, and hereditary pancreatitis (15).

Summary: Children need to be followed during their course of AP for local and systemic complications that may include organ dysfunction, acute fluid collections and subsequently walled-off necrosis or pseudocysts. Overall pediatric patients with acute pancreatitis have a good prognosis with very low rate of mortality, but up to 15–35% rate of recurrence is reported.

Recommendation 3: Children with acute pancreatitis should receive close follow-up by a health care provider to identify early or late complications, or recurrence.

24/24 = 100% agreement with recommendation.

Voting results: Strongly agree = 18; agree = 6; neutral = 0; disagree= 0; strongly disagree= 0.

4. Summary of Recommendations

Please refer to Table 1 for a summary of the above recommendations for the management of pediatric AP accepted by at least 75% of the voting group. Only one recommendation, relating to antibiotic use in documented infected necrosis (Recommendation 2eii) did not reach sufficient level of agreement to be accepted, with only 16/24 (67%) voters agreeing

with the statement, and 2 voters being “neutral”, 4 voters disagreeing, and 2 voters abstaining. As voting was conducted in an anonymous fashion without requesting explanation for voting category selected, the reason for the disagreement cannot be confirmed. However, this topic had been debated at the October 2016 face-to-face meeting, with certain members advocating for antibiotic prophylaxis for severe pancreatitis episodes involving pancreatic necrosis without necessarily infected necrosis.

5. Future Directions

The differences in etiologies leading to adult versus pediatric AP, the differences in physiology between children and adults, and the increased co-existence of extra-pancreatic illnesses in many adult patients would be anticipated to lead to different outcomes in children versus adults with AP. Findings from AP studies in adult patients thus cannot be justified as appropriate surrogate for managing children with AP. A 2014 manuscript by Abu-El-Haija et al highlighted areas in need of research within the realm of management of pediatric AP(4). Areas of note included the need for robust studies that are prospectively designed to answer fundamental questions on optimizing imaging modalities, pain medications, rehydration strategies, route and timing of enteral nutrition, surgical interventions, and prognostication scores in pediatric pancreatitis.

This current review of the available literature in pediatric AP highlights the ongoing lack of high-quality research focusing on pediatric AP in the great majority of spheres mentioned above. Some limited evidence has been published regarding fluid management and early introduction of enteral nutrition in children with AP, and prognostication of severity in pediatric AP. Recommendations on monitoring patients with AP relate to the care of sick children in general, and are not specific to AP. Pain management similarly has not focused on children with AP. Other than one retrospective case series on biliary pancreatitis timing of cholecystectomy, surgical recommendations remain extrapolations from adult literature. Very few studies are published on use of protease inhibitors. Experience with ERCP and EUS in pediatric AP remains limited. No pediatric AP-specific data are published regarding use of antibiotics, antioxidants, or probiotics. The lack of agreement on proposed recommendation 2eii relating to limiting use of antibiotics to only cases of documented infected pancreatic necrosis supports the need for further systematic research on use of antibiotics for AP. Certain authors stated monitoring recommendations were not sufficiently aggressive, leading to “neutral” votes cast. The authors wish to highlight the importance and necessity of supporting pediatric-specific research in the field of AP in all areas of management detailed within this manuscript.

6. Concluding Remarks

Due to the increased incidence of pediatric acute pancreatitis in recent years, pediatric specialists must be aware of the literature regarding its management. This clinical report reviews published evidence and provides recommendations for optimal management of AP in children, drawing upon adult literature, the limited pediatric studies and expert opinion in areas where pediatric data are lacking. To optimize pediatric AP outcomes, it will be critical to revisit these topics again in the near future when more pediatric focused, prospective studies in all aspects of pancreatitis management become available.

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WHAT IS KNOWN

- Pediatric acute pancreatitis (AP) incidence is increasing
- A subset of children develop local and systemic complications of AP
- No guidelines exist for management of pediatric AP in North America

WHAT IS NEW

- Recommendations for management of pediatric AP manifestations are provided, including aggressive early fluid administration, careful monitoring, pain control, early enteral nutrition, and indications for endoscopic and surgical procedures
- Evidence for use of antibiotics and protease inhibitors for pediatric AP is limited

TABLE 1

Summary Recommendations for Management of Acute Pancreatitis in Children

Topic	Recommendation
Diagnosis AP	<ul style="list-style-type: none"> • Diagnosis of pediatric acute pancreatitis (AP) should be as per previously-published INSPPIRE criteria. Diagnosis of AP in pediatric patients requires at least 2 of the following: (1) abdominal pain compatible with AP, (2) serum amylase and/or lipase values ≥ 3 times upper limits of normal, (3) imaging findings consistent with AP. • Initial imaging may be accomplished via transabdominal ultrasonography, with other imaging (CT, MRI) reserved for more complicated cases +/- tailored to suspected etiology • Based on most frequent etiologies and those for which therapeutic options exist, first attack of AP testing should include liver enzymes (ALT, AST, GGT, ALP, bilirubin), triglyceride level, and calcium level
Fluid Resuscitation	<ul style="list-style-type: none"> • Children with AP should be initially resuscitated with crystalloids, either with LR or NS in the acute setting. Based on assessment of hydration status/hemodynamic status, if evidence of hemodynamic compromise, a bolus of 10–20mL/kg is recommended • Children with diagnosis of AP should be provided 1.5–2x maintenance IV fluids with monitoring of urine output over the next 24–48h
Monitoring	<ul style="list-style-type: none"> • In patients admitted to an inpatient ward, vitals should be obtained at least every 4 hours during the first 48 hours of admission and during periods of aggressive hydration to monitor oxygen saturation, blood pressure and respiratory rate. Frequency to be adjusted based on clinical status. Abnormalities of vital signs should prompt specialist assessment • BUN, creatinine and urine output should be monitored routinely during the first 48 hours as marker of appropriate fluid management and to screen for acute kidney injury. Abnormalities should prompt nephrology assessment.
Pain management	<ul style="list-style-type: none"> • Intravenous morphine or other opioid should be used for acute pancreatitis pain not responding to acetaminophen or NSAIDs • Acute pain specialist services should ideally be consulted in cases of more severe pain to optimize pain management
Nutrition	<ul style="list-style-type: none"> • Except in the presence of direct contraindications to use the gut, children with mild AP may benefit from early (within 48–72 hours of presentation) oral/enteral nutrition (EN) to decrease length of stay and decrease risk of organ dysfunction • Parenteral nutrition (PN) should be considered in cases when EN is not possible for a prolonged period of time (longer than 5–7 days) such as in ileus, complex fistulae, abdominal compartment syndrome, to reduce the catabolic state of the body. Enteral nutrition should commence as soon as feasible, with a combination of EN and PN being superior to sole PN. • In cases of pancreatic laceration, fracture, or duct disruption, it is unclear whether oral/enteral feedings may be detrimental in the acute phase. This must be further studied.
Antibiotics	<ul style="list-style-type: none"> • Prophylactic antibiotics are not empirically recommended in severe AP • Antibiotic use is indicated only in cases of documented infected necrosis in AP
Proteases	<ul style="list-style-type: none"> • Anti-proteases cannot be recommended in the management of acute pancreatitis in children at this time
Antioxidants	<ul style="list-style-type: none"> • Antioxidants should not be considered standard therapy in the management of pediatric AP
Probiotics	<ul style="list-style-type: none"> • Probiotics cannot be recommended in the management of pediatric AP at this time. Highest-quality published adult evidence suggests they may be not only of no benefit, but increase mortality
Endoscopy	<ul style="list-style-type: none"> • Esophago-gastroduodenoscopy is not considered a standard diagnostic tool in pediatric AP at this time. Indication for its use should be determined on a case-by-case basis.

Topic	Recommendation
ERCP	<ul style="list-style-type: none"> The role of ERCP is limited in AP and depends on local expertise. ERCP is indicated in management of AP related to choledocholithiasis causing biliary pancreatitis, and for pancreatic duct pathologies such as ductal stones or ductal leaks
EUS	<ul style="list-style-type: none"> EUS is not considered a standard diagnostic tool in pediatric AP at this time. Indication for its use should be determined on a case-by-case basis
Surgery	<ul style="list-style-type: none"> Cholecystectomy safely can and should be performed before discharge in cases of mild uncomplicated acute biliary pancreatitis In the management of acute necrotic collections, interventions should be avoided and delayed, even for infected necrosis, as outcomes are superior with delayed (> 4 weeks) approach When drainage or necrosectomy is necessary, non-surgical approaches including endoscopic (EUS, and ERCP-assisted) or percutaneous methods are preferred over open necrosectomy or open pseudocyst drainage
Outcomes/Surveillance	<ul style="list-style-type: none"> Children with AP should receive close follow-up by a health care provider to identify early or late complications, or recurrence