Abstract

Objective: To describe the main epidemiological, clinical, diagnostic and treatment aspects of children with acute pancreatitis.

Sources: Systematic review of MEDLINE and SciELO databases in the last 5 years about acute pancreatitis in children, as well as consultation of relevant references on the texts obtained.

Summary of the findings: Cases of acute pancreatitis in children have received growing attention in recent years, and an increase in the number of cases has been reported in several studies. The main etiologies in children involve biliary disease, drug-induced pancreatitis, recurrent hereditary pancreatitis and trauma, and up to 30% of cases have no defined etiology. The diagnosis is based on the combination of clinical and laboratory aspects with the increase of acinar enzymes and radiologic tests. Initial support treatment, with proper volume replacement and correction of the metabolic disturbances, besides specific nutritional therapy, are the fundamental points in the handling of acute conditions. Long term complications are unusual, and mortality rates are inferior to the rates for the adult population.

Conclusions: The early diagnosis and the appropriate handling can contribute to a better outcome for the child with pancreatitis and to prevent the immediate and late complications related to the disease. More studies are required to better explain aspects related to the clinical and radiological diagnosis of pancreatitis in children, as well as aspects related to the nutritional therapy for this age group.


Introduction

Acute pancreatitis (AP) is defined as the histological presence of inflammation of the pancreatic parenchyma. It is a reversible process characterized by the presence of interstitial edema, infiltration by inflammatory cells and variable degrees of cellular apoptosis, necrosis and hemorrhage. The recurrent fibrotic and inflammatory processes may cause different degrees of dysfunction in the endocrine and exocrine pancreas or in both.

Although it is a well-known disease concerning its clinical and treatment aspects in the adult population, most...
of the recommendations in pediatrics related to diagnosis and key points of AP clinical handling, as well as the most appropriate form of introduction of the nutritional therapy, are derived from studies involving only adults. The diagnosis of AP in children has received growing attention in recent years, with a trend towards an increased incidence and with large differences when compared to the disease in the adult population, not only in etiological aspects but also in clinical features and treatment.3

The purpose of this review was to study the main epidemiological, clinical, diagnostic and therapeutic characteristics of AP in children, with a systematic review on medical literature, and the discussion of topics for future research in this field.

**Literature search criteria and methods**

For the choice of the articles analyzed in this review, a systematic review of MEDLINE and SciELO databases was performed. Since the main part of the texts on nutritional aspects of AP are discussed separately from the other clinical aspects, there was a parallel research with other descriptors only considering topics related to the introduction of the nutritional therapy and the nutritional complications of the disease. Thus, the following criteria were used:

- **Studied period**: articles published on MEDLINE from July 2006 to July 2011; on SciELO, between August, 1980 and August, 2011. Relevant references and historical quotes, as well as extremely important studies within the context of the review were analyzed in the same way, regardless of the publication dates.
- **Studies design**: The review included prospective and retrospective cohort studies, systematic and non-systematic reviews and clinical trials, containing a description of clinical aspects of AP in patients with up to 18 years old completed; except for case reports of drug-induced AP or articles on nutritional therapy introduction, because of the shortage of such publications on the pediatric population, in which age groups were not limited. The review considered articles written in Portuguese, English, French and Spanish.
- **Exclusion criteria**: studies involving adult population (except for the cases above mentioned), editorials, reports of isolated cases of AP, book chapters and articles found by the search terms but were not related to the subject of the review.
- **Definitions**: The review studied articles that defined AP as the acute inflammation of the pancreatic parenchyma, with typical symptomatology, such as abdominal pain, nausea and vomiting associated to the increase of pancreatic acinar enzymes three times above the reference value and/or alterations in the radiological exams compatible with AP.1

- **Evaluated outcomes**: Associated morbidity and mortality, acute and chronic complications, length of hospital stay, pulmonary diseases and formation of pancreatic pseudocysts.

**Search and results mechanisms**

The study conducted four search mechanisms on the databases mentioned, followed by their respective results:

a) **SciELO. Terms used in the search**: pancreatitis OR pancreatitis AND children OR pediatrics (All Indexes); two case reports.

b) **SciELO. Terms used in the search**: pancreatitis OR pancreatitis AND nutrition OR nutrition (All Indexes); two articles, one not related to the subject of research and another already included in the MEDLINE search.

c) **MEDLINE. Terms used in the search**: acute (All Fields) AND pancreatitis (MeSH Terms) OR pancreatitis (All Fields) AND nutritional status (MeSH Terms) OR nutritional (All Fields) AND status (All Fields) OR nutritional status (All Fields) OR nutrition (All Fields) OR nutritional sciences (MeSH Terms) OR nutritional (All Fields) AND sciences (All Fields) OR nutritional sciences (All Fields) AND child (MeSH Terms) OR child (All Fields) OR children (All Fields) AND 2006/08/17 (PDat) : 2011/08/15 (PDat); 25 results, and 24 were excluded according to the exclusion criteria explained.

d) **MEDLINE. Terms used in the search**: acute (All Fields) AND pancreatitis (MeSH Terms) OR pancreatitis (All Fields) AND child (MeSH Terms) OR child (All Fields) OR children (All Fields) AND therapy (Subheading) OR therapy (All Fields) OR treatment (All Fields) OR therapeutics (MeSH Terms) OR therapeutics (All Fields) AND acute (All Fields) AND pancreatitis (MeSH Terms) OR pancreatitis (All Fields) AND child (MeSH Terms) OR child (All Fields) OR children (All Fields) AND therapy (All Fields) AND 2006/07/25 (PDat): 2011/07/23 (PDat); 243 results, and 68 studies were analyzed, as described below.

Figure 1 illustrates the obtained results, as well as the exclusion criteria of the articles during the research.

**Epidemiologic aspects**

The broader knowledge of the clinical aspects and the growing level of suspicion of AP cases (leading to growing requests for amylase and lipase biochemical tests), as well as the progressive increase in the use of drugs that may induce AP as an adverse effect, have led to a progressive increase in the number of diagnosis of the disease in recent years.4 Another possible explanation for the growing incidence of AP is the increase in cases of children with systemic diseases that affect the pancreas secondarily. It is claimed that, due
to this fact, the referral of patients to tertiary and school hospitals, where most of the clinical studies are conducted, contributes to a higher identification of the cases of AP. Fagenholz et al. studied retrospectively the medical records of the disease in the United States and found that, in the general population, the number of AP cases has doubled from 1998 to 2002, from 101,000 cases to 202,000 new cases every year in the country, according to records of the national hospital discharge survey. Between 1988 and 2003, 645 cases were diagnosed in children and adolescents, with an incidence of 0.1 new cases per 1,000 inhabitants. The authors do not make considerations regarding the findings in the pediatric population and mention that the study was limited to a research based on diagnosis through the code of International Classification of Diseases (ICD), with no criteria to define cases of pancreatitis. Nydegger et al. assessed, also retrospectively, the diagnosis of AP in children at an Australian hospital from 1993 to 2002. During this period, 279 cases of the disease were diagnosed, with mean age of 10 years, and 74.9% of cases had an attributed etiology (mainly trauma, metabolic and systemic diseases and drugs). The authors compared the incidence rate in the first five years of the studied period with the last five years, and found an increase of approximately seven new cases per year from 1998 to 2002 when compared to the period from 1993 to 1997. Another relevant epidemiological study examined the incidence of AP at the Children’s Hospital of Pittsburgh, through a retrospective study of

Figure 1 - Diagram flow of the obtained results
Morinville et al.5 Between 1993 and 2004, 1,021 patients were discharged with a diagnosis of AP, with 731 new cases, with an increase in new cases per year from 28 in 1993 to 141 in 2004. The incidence calculated in this work has increased over the same period, from 2.4 to 13.2 new cases per 100,000 children.

**Etiology of acute pancreatitis in children**

Unlike the adult population, in which the etiology of AP secondary to biliary disease and alcoholism is well defined in most cases, in children the causes are more variable, including various systemic conditions and, increasingly frequent, secondary to medication. According to most texts, the five leading causes of AP in children, in order of frequency, are: biliary diseases, drug-induced AP, idiopathic AP, systemic diseases and trauma, followed by metabolic, hereditary and infectious diseases.8

**Acute biliary pancreatitis**

Similarly to what happens in adults, diseases of the biliary tract, whether represented by biliary gallstones, biliary sludge or anatomical anomalies of the pancreas and its ductal system (such as sphincter of Oddi dysfunctions or pancreas divisum), are important causes of AP, corresponding to 10 to 30% of cases;3,4 however, in retrospective cohort studies, the incidence of biliary AP may be higher, reaching up to 50%.9 The biliary sludge (excess of bile salts in the gallbladder) can represent up to 30% of the cases of biliary obstruction in children, unlike adults, whose obstruction is almost only due to the biliary lithiasis or tumors with compressive characteristics. However, the casual relation between the presence of the biliary sludge and the occurrence of AP is not totally determined, what makes some authors prefer not to include such condition as an etiology of AP in children.10 Besides, except for some cases of recurrent AP, cholecystectomy is not routinely indicated for patients with AP and diagnosed biliary sludge, as opposed to patients with cholelithiasis and AP, whose surgery has to be performed preferably in the first 2 weeks after resolution of the acute condition.11

Other diseases of the biliary tree, of surgical management, may also be involved in the etiology of AP in children, such as duodenal duplication and congenital pancreatic anomalies (annular pancreas); in the later, a the second portion of the duodenum is partially or completely surrounded by pancreatic tissue, producing symptoms of duodenal obstruction.12-14

**Hereditary recurrent acute pancreatitis: genetic aspects**

The recurrent forms of AP tend to be more associated to malformations of the pancreatobiliary tract, hereditary pancreatitis and cystic fibrosis.15-17 Sánchez-Ramirez et al.18 observed 36 children diagnosed with AP and 19 with recurrent pancreatitis, concluding that, in approximately 35% of the cases the cause was idiopathic, even after thorough investigation, as pointed out in previous studies that describe values between 10-20% of idiopathic AP in children.19,20 Still, recent evidence suggested that a significant portion of cases of idiopathic pancreatitis in children is related to various genetic mutations,18,21 directly responsible for the occurrence of the disease or predisposing it, many of which are located on the long arm of chromosome 7 (7q35), where many genes involved with the transcription and regulation of trypsinogen are located.22

Among the genetic diseases, cystic fibrosis is the most known to lead to chronic pancreatitis in 1-2% of cases and is often responsible for cases of recurrent AP in pancreatic-sufficient patients, what happens in 10-17% of cases, and it often corresponds to the first manifestation of the disease with clinical implications.19 Over 1,000 mutations of the cystic fibrosis transmembrane conductance regulator (CFTR) gene were described15,18,23 as the cause of the autosomal recessive disorder, as they impair the function of the cyclic adenosine monophosphate-regulated chloride channels and the secretion of sodium bicarbonate, which, together, change the balance in the dilution and alkalinization of the pancreatic juice, triggering the formation of intraductal protein plugs by the accumulation of more viscous fluid and influencing the activation of intrapancreatic enzymes and subsequent autodigestion of the parenchyma. It is estimated that even heterozygous individuals for the CFTR gene mutations have a 40-fold higher risk of developing chronic pancreatitis.22 Still, it is suggested that mutational patterns of the CFTR gene, not necessarily related to cystic fibrosis, could predispose patients to developing recurrent AP, especially in the presence of mutations in other related genetic locations, as, for instance, in the cationic trypsinogen gene (PRSS1) and in the serine protease inhibitor Kazal type 1 (SPINK1).

Another condition more recently studied is the hereditary chronic pancreatitis (HCP), described for the first time in 1952 by the researchers Comfort & Steinberg.24 It is a chromosome abnormality of the 7q35, location of the PRSS1 gene, which is a site of nine currently known mutations. The mutation of largest association to HCP and which is widely known is R122H, described by Whitcomb,25 followed by the N29I mutation, also of the same gene. Others, such as A16V, D22G and K23R seem to have weaker association with the disease, although they are also described in medical literature.

The product encoded by the PRSS1 gene, cationic trypsinogen, is the predominant isoform in the pancreatic juice of humans. Mutations on this gene are related to the increased conversion of trypsinogen to intrapancreatic trypsin, as well as the reduction of its autolysis, with an
increase in its stability.\textsuperscript{26} It is estimated that approximately 60-80\% of patients with hereditary pancreatitis are carriers of the pathogenic mutations of PRSS1. More recently, the description of the mutation on the PRSS2 gene, especially the G191R variant, which encodes another trypsinogen isoform, anionic, was associated to the protection against chronic pancreatitis, once it seems to produce a hypersensitized protein, the autocatalytic proteolysis, when activated still in the pancreas.

The HCP is clinically diagnosed by the presence of two first-degree relatives or, at least, three second-degree relatives, in two or more generations, with chronic pancreatitis, for which there is no other etiology, and has autosomal dominant inheritance,\textsuperscript{27} with estimated 80\% penetrance, whose onset usually occurs before age 20 and, in most cases, before age 10. It is estimated that 50\% of patients with this disease progress to chronic pancreatitis in the long term and that the cumulative risk of developing pancreatic ductal adenocarcinoma is 40\% (around age 70), compared to a significantly lower risk for the general population (about 1\%). From the analysis of data from the European registry of hereditary pancreatitis and pancreatic cancer, Howes et al.\textsuperscript{28} have demonstrated that about 81.25\% of families with a history of hereditary pancreatitis had a mutation in the PRSS1 gene, 52\% positive for the R122H mutation and 21\% for N29I. Other genetic defects, also related to the occurrence of recurrent acute and chronic idiopathic pancreatitis, may occur, among which we highlight the ones from the SPINK1 gene, located on chromosome 5 (5q32), particularly the p.N34S mutation.

**Need for genetic counseling**

The option of performing genetic testing to detect mutations that may relate to the occurrence of recurrent AP in children still remains little available, mainly due to the high cost involved in obtaining specific kits,\textsuperscript{19} but it may be discussed, in the effort to attain more sources to confirm the diagnosis of hereditary pancreatitis. In this case, the Consensus Committees of the European Registry of Hereditary Pancreatic Diseases, the Midwest Multi-Center Pancreatic Study Group and the International Association of Pancreatologists recommend testing for children younger than 16 years with two or more episodes of AP of unknown etiology; one episode of AP of unknown etiology that requires hospitalization due to severity; one episode of AP and one relative who carries mutation associated to hereditary pancreatitis; recurrent abdominal pain without etiologic diagnosis in which hereditary pancreatitis is a probable differential and, finally, in the cases of idiopathic chronic pancreatitis in which hereditary pancreatitis is a likely differential diagnosis. For the individuals with positive results in molecular tests for mutations related to the disease, it is recommended to provide long-term observation, besides genetic counseling, when at older ages with reproductive interest and psychological support for the families.\textsuperscript{26}

**Drug-induced acute pancreatitis and to systemic disease**

The real incidence of drug-induced AP is usually estimated from case reports or by results of studies conducted with other purposes. Similarly, a reliable diagnosis of this condition is often difficult, considering the absence of diagnostic exams that establish an unequivocal cause/effect relation.\textsuperscript{29} In order to establish such relation, it is normally necessary that AP occurs during the administration of an specific drug, and all other more common causes are excluded during the investigation; besides, the symptoms of the disease must resolve with the discontinuation of the medication and recur after new administration of the suspect drug.

In pediatrics, the more recent case reports include the valproic acid and the L-asparaginase, used in the initial treatment of acute lymphocytic leukemia, as the most commonly involved drugs in cases of secondary AP. Systemic diseases such as erythematous lupus, celiac disease and Henoch-Schonlein purpura are also reported as causes of AP. Each drug or systemic disease presents peculiarities concerning the nature and the extent of pancreatic involvement, and the mechanism of glandular damage. Tables 1 and 2 illustrate the main reports retrieved in this review,\textsuperscript{30-53} as well as the clinic characteristics of the studied patients and the relevant aspects of the discussion of each study, be it in AP associated to drugs or to systemic diseases.

**Acute pancreatitis induced by trauma**

The presence of trauma, more specifically secondary to motor vehicle crashes, sports injuries, run-overs, accidental falls and sexual abuse in children, may represent 10 to 40\% of the etiology of the cases of AP.\textsuperscript{3,54} Because of their retroperitoneal location, the traumatic pancreatic injuries may be difficult to diagnose, and therefore the reported incidence of AP secondary to trauma may be underestimated. Moreover, the difficult and delayed diagnosis may contribute to a possible higher morbidity of children with traumatic AP.\textsuperscript{55} The most commonly used diagnostic methods are based on imaging such as abdominal computer tomography (CT) with contrast and/or ultrasonography (US), besides the intraoperative inspection of the organ during exploratory laparotomy.

**Idiopathic pancreatitis secondary to infection**

Despite the increasing improvement in the diagnostic methods and the greater recognition of the etiology of AP in children, up to 30\% of cases may not have a specific cause diagnosed.\textsuperscript{3,56} Many patients with a diagnostic of AP have in their history symptoms which are compatible to
Table 1 - Reviewed cases of drug-induced acute pancreatitis and their main clinical and laboratory characteristics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Author</th>
<th>Population and dose used</th>
<th>Enzymes dosing</th>
<th>Relevant data</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone</td>
<td>Beaufort et al., 2006</td>
<td>6 years, female</td>
<td>Amylase 1,660 U/L Lipase 2,736 U/L</td>
<td>Patient diagnosed with mitochondrial disease that may cause chronic pancreatitis and GH deficiency</td>
<td>Complete recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GH partial deficiency</td>
<td>Dose 25 mcg/kg/day</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2006</td>
<td>Lipase 2,736 U/L</td>
<td>Panhypopituitarism after resection of craniopharyngioma Changes in lipid metabolism by hyperphagia caused by hypothalamic damage may cause the disease Increased secretion of pancreatic enzymes due to GH stimulation</td>
<td>Complete recovery in 12 days without relapse</td>
</tr>
<tr>
<td></td>
<td>Faienza et al., 2009</td>
<td>13 years, female</td>
<td>Amylase 543 U/L Lipase 586 U/L</td>
<td>Changes in lipid metabolism by hyperphagia caused by hypothalamic damage may cause the disease</td>
<td>Complete recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 33 mcg/kg/day</td>
<td>Dose 33 mcg/kg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2009</td>
<td>Lipase 586 U/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic Acid</td>
<td>Gerstner et al., 2007</td>
<td>16 children Mean serum level 70 mg/dL</td>
<td>Mean amylase 1,242 U/L Mean lipase 2,381 U/L</td>
<td>Estimated incidence of 1 to 40,000 Causative mechanism is little known (idiosyncrasy, direct toxic effect by depletion of superoxide dismutase, catalase or glutathione-peroxidase)</td>
<td>15 patients with complete recovery; one relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dose 25 mcg/kg/day</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>2009</td>
<td>Lipase 2,381 U/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ózadin et al., 2008</td>
<td>11 years, male</td>
<td>Dose 25 mg/kg</td>
<td>Amylase 742 U/L (24-125)</td>
<td>Recurrence of AP may occur in up to 75% of cases if the drug is prescribed again</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Guevara-Campos et al., 2009</td>
<td>7 years, female</td>
<td>Dose 15 mg/kg</td>
<td>Amylase 400 U/L (20 - 112)</td>
<td>Toxicity may be related to two active metabolites- 2-valproic acid and 4-valproic acid</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Garg et al., 2010</td>
<td>7 years, female</td>
<td>Amylase 1,431 U/L</td>
<td>Rare adverse effect, but of probable immune-mediated origin Attention for abdominal pain in patients in immunosuppression for collection of liver enzymes</td>
<td>Complete recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 1.5 g/m²/day</td>
<td>Dose 1.5 g/m²/day</td>
<td></td>
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</tr>
<tr>
<td>Tigecycline</td>
<td>Prot-Labarthe et al., 2010</td>
<td>8 years, male</td>
<td>Lipase 134 U/L Normal amylase</td>
<td>No recommendations for pediatric patients First case report Association with antibiotics – causal relation?</td>
<td>Complete recovery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 100 mg/day</td>
<td>Dose 100 mg/day</td>
<td></td>
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<tr>
<td>Asparaginase</td>
<td>Flores-Calderón et al., 2009</td>
<td>266 children receiving asparaginase for acute lymphocytic leukemia Mean Age 8.6 years Dose 6,000 to 10,000 U/m²</td>
<td>Mean Amylase 746 U/L Mean lipase 1,508 U/L</td>
<td>Incidence of AP in 6.7% (18 cases) Onset of symptoms: mean of 9 days after last dose 10 patients developed chronic pancreatitis</td>
<td>14 patients needed PPN Two patients developed chronic pancreatitis No deaths</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dose 6,000 to 10,000 U/m²</td>
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<tr>
<td>Kearney et al., 2009</td>
<td>Retrospective cohort of 403 children with ALL</td>
<td>Mean Age - 7.1 years Dose 25,000 U/m²</td>
<td>Mean amylase 553 U/L Mean lipase 1,143 U/L</td>
<td>Incidence of PA - 7% (28 patients) Onset of symptoms: mean of 4 weeks after last dose 2.4 times higher risk in children aged 10-18 years</td>
<td>18% developed pseudocysts No deaths or long-term sequelae</td>
</tr>
<tr>
<td>Treppongkaruna et al., 2009</td>
<td>Retrospective Cohort of 192 children with ALL</td>
<td>Mean Age - N/E Dose 10,000 to 25,000 U/m²</td>
<td>Mean amylase 5,775 U/L Mean lipase 236 U/L</td>
<td>Incidence of AP – 7.3% (14 patients) Multiple analysis showed only high doses of the drug as an independent risk factor for AP</td>
<td>Eight (57%) deaths</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia; AP = acute pancreatitis; GH = growth hormone; N/E = not evaluated; PPN = prolonged parenteral nutrition.
Table 1 - Reviewed cases of drug-induced acute pancreatitis and their main clinical and laboratory characteristics (continuation)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Author</th>
<th>Population and dose used</th>
<th>Enzymes dosing</th>
<th>Relevant data</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asparaginase</td>
<td>Vrooman et al.,</td>
<td>42 children receiving</td>
<td>N/E</td>
<td>Incidence of pancreatitis - 7% (similar to the incidence of pancreatitis due to E. coli-derived asparaginase)</td>
<td>N/E</td>
</tr>
<tr>
<td></td>
<td>2010</td>
<td>enzyme derived from</td>
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<td></td>
<td></td>
<td>Erwinia sp and history</td>
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<tr>
<td></td>
<td></td>
<td>of allergy to E. coli-derived asparaginase</td>
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<tr>
<td></td>
<td></td>
<td>Median age 5.5 years</td>
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<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose 25,000 U/m²</td>
<td></td>
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</tr>
<tr>
<td>Propofol</td>
<td>Crawford et al.,</td>
<td>Five children with</td>
<td>N/E</td>
<td>Questionable causal relation – most held adjuvant treatment with asparaginase and 6-mercaptopurine</td>
<td>Complete recovery</td>
</tr>
<tr>
<td></td>
<td>2009</td>
<td>leukemia (mean age 10</td>
<td></td>
<td>Probable cause: changes in lipid metabolism leading to hypertriglyceridemia,</td>
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<tr>
<td></td>
<td></td>
<td>years)</td>
<td></td>
<td>trypsinogen activation and capillary obstruction by chylomicrons</td>
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<tr>
<td></td>
<td></td>
<td>Mean of 19 doses of</td>
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<tr>
<td></td>
<td></td>
<td>propofol each for various procedures</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Mean dose 3 mg/kg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Bai et al.,</td>
<td>Retrospective cohort of</td>
<td>N/E</td>
<td>55 children (25.6%) with a diagnosis of drug-related pancreatitis</td>
<td>Complete recovery</td>
</tr>
<tr>
<td></td>
<td>2011</td>
<td>271 cases of pancreatitis</td>
<td></td>
<td>Most frequent comorbidities were epilepsy, Crohn disease and acute lymphoid leukemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean age 12.8 years</td>
<td></td>
<td>Most involved drugs – valproic acid, mesalazine and asparaginase</td>
<td>18% of patients needed parenteral nutrition</td>
</tr>
</tbody>
</table>

ALL = acute lymphoblastic leukemia; AP = acute pancreatitis; GH = growth hormone; N/E = not evaluated; PPN = prolonged parenteral nutrition.

previous viral infections (such as fever, cough, runny nose or diarrhea), however, it is difficult to establish causal relations between both). Some agents, such as the rotavirus and the varicella virus, have been associated with isolated cases of AP in children, as illustrated in Table 2.

Diagnosis of acute pancreatitis in children

Clinical and laboratory diagnosis

The diagnosis of AP in children occurs, in most cases, through the combination of clinical history and biochemical and imaging tests. Similarly to what happens in adults, abdominal pain is the most common symptom in children, occurring in 80 to 95% of the cases, and the most common locations of pain are as follows: epigastric (62-89%), diffuse (12-20%), in the back (< 10%) and, in about 5% of cases, with radiation to the dorsal region. Nausea and vomiting, as well as abdominal distention, may be present, respectively, in 40 to 80% of the cases and 21 to 46% of cases.

In 1992, diagnostic criteria were developed for AP at a conference in Atlanta, considering the adult population. Traditionally, these criteria are also used for the diagnosis in children and include at least two of the three following criteria: abdominal pain, levels of amylase or lipase three times higher than the reference values and/or radiologic findings that corroborate the clinic diagnosis. Other symptoms may also be present, such as jaundice, fever, ascites, pleural effusion, abdominal distension and adynamic ileus. In some cases, there may be initial symptoms such as palpable abdominal mass corresponding to pancreatic pseudocysts.

The dosage of pancreatic acinar enzymes, amylase and lipase, has limitations in the diagnosis of AP regarding the sensitivity and the specificity, as well as for the occurrence of false-positive results in both dosages. The amylase dosage has sensitivity ranging between 50 to 85%, while in almost 100% of cases of AP lipase dosages are increased. These distinctions may be attributed to differences in the expression
<table>
<thead>
<tr>
<th>Illness or medical condition</th>
<th>Author</th>
<th>Studied population</th>
<th>Enzymes dosing</th>
<th>Relevant data</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typhoid fever</td>
<td>Asano et al., 2007(^43)</td>
<td>Female, 4 years</td>
<td>Amylase 782 U/L</td>
<td>Pancreatitis may be asymptomatic in up to 37.5% of cases. More common in the septicemic phase (late)</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Burkitt lymphoma</td>
<td>Silva et al., 2008(^44)</td>
<td>Male, 13 years</td>
<td>Amylase 339 U/L</td>
<td>Infiltration of the gastrointestinal tract and body of the pancreas. Incidence unknown due to the scarcity of cases reported</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Henoch-Schonlein Purpura</td>
<td>Soyer et al., 2008(^45)</td>
<td>Female, 3 years</td>
<td>Amylase 128 (0-53) Lipase 102 (0-60)</td>
<td>Abdominal pain main precede the rash in the disease in up to 36% of cases. Pancreatitis may be initial finding. Unspecific symptoms. Only two cases reported.</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Bultron et al., 2009(^46)</td>
<td>Male, 9 years</td>
<td>Amylase 351 U/L Lipase 1,657 U/L</td>
<td>First case reported in children. Previous adult reports show risk up to 3.3 times higher in celiac patients. Triggering factors – malnutrition and papillary stenosis by duodenal inflammation</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Erythematous systemic lupus</td>
<td>Rose et al., 2009(^47)</td>
<td>Female, 14 years</td>
<td>Amylase 1,472 U/L Lipase 3,316 U/L</td>
<td>AP may be the initial manifestation of lupus in children. Incidence of 0.4 to 1.1 case/1,000 patients with lupus. AP may be induced by the immunopressive drugs or vasculitis and/or disease-induced thrombosis.</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Measles</td>
<td>Fusilli et al., 2009(^48)</td>
<td>Female, 2 years</td>
<td>Lipase 310 U/L</td>
<td>Rare event secondary to the disease, difficult to estimate the incidence.</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Chickenpox</td>
<td>Franco et al., 2009(^49)</td>
<td>Female, 6 years</td>
<td>Amylase 1,757 U/L</td>
<td>Viral etiology in AP may reach 10%, and the most common virus are mumps and coxsackievirus</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Sexual abuse</td>
<td>Oliveira et al., 2010(^50)</td>
<td>Female, 8 years</td>
<td>Amylase 3,258 U/L</td>
<td>Probable mechanism related to blunt abdominal trauma. Traumatic AP requires surgery and evolves more commonly with pseudocysts</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Crohn’s Disease</td>
<td>Briem-Richter et al., 2010(^51)</td>
<td>Female, 14 years</td>
<td>Amylase around 1,000 U/L Lipase around 1,500 U/L</td>
<td>AP mechanisms - duodenal and biliary obstruction by inflammation; possible involvement of immunosuppressive drugs or idiopathic</td>
<td>Formation of giant pseudocyst Need for surgery to drain Complete recovery</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Parri et al., 2010(^52)</td>
<td>Male, 2 years</td>
<td>Amylase 1,037 U/L Lipase 236 U/L</td>
<td>AP Mechanisms – direct pancreatic toxicity by the virus; dysfunction of the intestinal barrier by diarrhea</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Burns</td>
<td>Rivero et al., 2011(^53)</td>
<td>Retrospective cohort in 2,699 children hospitalized with burns</td>
<td>N/E</td>
<td>Number of cases of AP in burned patients - 13 (0.05%). After autopsy - increase of the rate to 0.17%. Survival - 69% (patients without AP - 87%). Comorbidities impact significantly on mortality rates.</td>
<td>Mortality 31%</td>
</tr>
</tbody>
</table>

N/E = not evaluated.
of the pancreatic enzymes during the first months of life – both the expressions of amylase and lipase increase after birth, and the increase in the expression of amylase occurs at a lower pace. Besides that, other systemic diseases may cause increase in the enzyme levels – particularly in the case of amylase, elevations may be attributed to non pancreatic causes (such as the salivary glands) or to the reduction in enzymatic clearance by the kidneys. The levels of lipase may be falsely increased in cases of pancreatic neoplasms, esophagitis, acute cholecystitis, acute renal failure and hypertriglyceridemia.\textsuperscript{58} Table 3 illustrates the main causes of false-positive results for serum amylase.\textsuperscript{3,59,60}

<table>
<thead>
<tr>
<th>Location</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal causes</td>
<td>Biliary tract disease</td>
</tr>
<tr>
<td></td>
<td>Peptic ulcer</td>
</tr>
<tr>
<td></td>
<td>Acute appendicitis</td>
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<td></td>
<td>Pancreatic cancer</td>
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<td>Ruptured ectopic pregnancy</td>
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<td>Prostate or ovarian neoplasms</td>
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<tr>
<td>Non-abdominal causes</td>
<td>Mumps or parotitis</td>
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<td></td>
<td>Trauma to the salivary glands</td>
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<td>Parotid ductal obstruction</td>
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<td></td>
<td>Pneumonia</td>
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<td>Pulmonary embolism</td>
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<td></td>
<td>Acute myocardial infarction</td>
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</tbody>
</table>

\textbf{Diagnostic imaging}

Diagnostic imaging plays a crucial role in the evaluation of cases of AP and chronic pancreatitis in all age groups.\textsuperscript{61} The abdominal US and the abdominal CT scans remain as the most used methods; however, the role of magnetic resonance imaging (MRI) associated to cholangiopancreatography has been increasingly discussed as an elective exam in the suspicion of diagnosis, due to the absence of radiation and invasiveness, and is gradually replacing endoscopic retrograde cholangiopancreatography (ERCP).

\textbf{Abdominal ultrasonography}

It is usually the initial modality of imaging evaluation when the diagnosis of AP is suspected in children. Some characteristics facilitate evaluation by US in children when compared to adults, such as smaller size of the patient, smaller fat tissue and prominence of the left hepatic lobe. In studies with adults, US has around 65% sensitivity for the diagnosis of AP. In most cases of AP, the pancreas is enlarged and hyperechoic in relation to the liver; however, as this is the normal appearance of the organ even in patients without AP, this fact is not relevant in diagnosis.\textsuperscript{62} Other alterations may include an increase in the diameter of the body of the pancreas and the pancreatic ducts.\textsuperscript{63} The US is also useful in the evaluation of the pancreatic pseudocysts, which normally have anechoic appearance with well-defined borders and posterior sonographic enhancement.\textsuperscript{64} Recently, the use of intravenous contrast associated to the US has shown good accuracy in the diagnosis of pancreatic necrosis, similarly to the results obtained with abdominal CT.\textsuperscript{65}

\textbf{Abdominal tomography}

It is also one of the most widely used methods in the diagnosis of AP, considering the wide access, the fact that the exam is not invasive and the familiarity with the interpretation of images. However, CT lacks sensitivity at the diagnosis of ductal changes and more subtle changes of the pancreatic parenchyma, besides the high load of radiation exposed to the patient.

CT findings include an increase in pancreatic size with ill-defined borders, peripancreatic fluid and possible areas of lower density or enhance after contrast, which may indicate necrosis.\textsuperscript{66} Besides these findings, one can find a diffuse enlargement of the gland with loss of lobular architecture, associated with iso or hypoattenuating parenchyma with
narrowed or nondilated pancreatic ducts. Comparing the CT with the US, CT has greater sensitivity for the diagnosis of AP, especially in the early stages, besides being able to better evaluate the extent of pancreatic necrosis, peripancreatic fat inflammation and the thickening of the initial segments of the small bowel, which can also be visualized.

Magnetic resonance cholangiopancreatography
This exam has the advantages of not exposing the patient to radiation, as well as providing important diagnostic information in the initial stages of AP. The morphology and distribution of the pancreatic ducts are better examined with the MRI. Its main limitations lie in the small diameters of the ducts in children and the frequent need for sedation, considering the greater length of the exam and the minimization of possible movement artifacts.

MRI has an important role in patients with AP secondary to anatomic and/or obstructive malformations that require surgical correction, such as cysts in the choledochal ducts and anomalous pancreaticobiliary junction. However, the small availability of this resource, the good results with more accessible exams (such as US and CT) and the reasons above mentioned hinder the widespread use of MRI for the initial diagnosis of AP in children, and more research is needed to validate it.

Endoscopic retrograde cholangiopancreatography
This exam has the advantages of not exposing the patient to radiation and allowing the visualization of the whole biliary tree.67 Besides, the complications rates are significantly higher when compared to other exams, especially if therapeutic measures are included during the exam and if manometry is applied to biliary and pancreatic sphincters, reaching up to 17%. Furthermore, the need to obtain deep sedation or general anesthesia to perform the procedure in children is almost universal. The most common indication for ERCP is biliary AP. ERCP is the appropriate therapeutic modality in patients with recurrent AP or with pancreatic pseudocysts. The classic findings in AP include focal, segmental or diffuse narrowing of the pancreatic ducts, without visualization of collateral branches.

Treatment of acute pancreatitis
General measures
The early recognition of cases of AP is fundamental to introduce the appropriate therapeutic and supportive measures, so as to reduce the morbimortality of the patients with the disease. The most important aspects in the handling of AP are hydration, analgesia and nutrition.

In adult patients, there are studies that demonstrate the association between hypovolemia and hypotension at admission of the patient with higher mortality. Hypovolemia, particularly in patients with severe AP, is the result of great increase in endothelial barrier permeability as a consequence of the systemic inflammatory response syndrome that occurs in AP.

This way, initial fluid replenishment minimizes the organic lesion by ischemia and reperfusion, restoring, thus, intravascular volume and improving the supply of oxygen to the tissues. It is recommended the rapid hydration of children who present some degree of dehydration at physical examination or, especially, hypotension, which tends to be rare and late in this group of patients, with crystalloid solution, preferably physiological saline solution (for its higher osmolarity when compared to Ringer Lactate), in aliquots of 20 mL/kg every 20-30 minutes, with frequent subsequent evaluations, until the signs of dehydration are reversed at the physical exam and parameters such as diuresis (above 1 mL/kg/hour), heart rate, pulse and capillary refill are normalized.

For patients requiring saline maintenance, whether because of low oral ingestion or by mandatory fasting until installation of parenteral nutrition (PN), isotonic solutions are recommended, with hydric offer between 80 and 100% of basal hydric need, calculated according to the rule of Holliday-Segar, and with sodium concentrations between 135 e 140 mEq/L. The glucose concentration should not exceed 8 g/100 kcal, and the patient should be constantly monitored in order to avoid hyperglycemia. Hyponatremia is a very common metabolic disorder in hospitalized children, and the secretion of antidiuretic hormone is stimulated by situations such as abdominal infections, pain, nausea and the use of opioid analgesics. Therefore, solutions with osmolarity based on the rule of Holliday-Segar should be avoided, at the risk of increased water retention and dilutional hyponatremia. The other electrolyte recommendations, according to the rule, should be kept and individualized for each case.

Abdominal pain is highly prevalent in patients with AP, and it is the main symptom that requires initial treatment. Ordinary analgesics may be insufficient, considering the common high intensity of pain, so constant reassessment of pain is necessary in children. Opioids may be necessary; however, the use of maximum doses of medicaments should be avoided, due to the occurrence of nausea and vomiting, besides the contraction of the digestive sphincters. Tramadol can be used at 1 mg/kg/dose up to four times a day, diluted in saline solution and in minimum infusion duration of 20 minutes.

Antibiotic prophylaxis, as well as the use of adjuvant medications in the treatment of AP, such as somatostatin analogues and corticosteroids, should not be routinely used, considering the absence of studies and clinical trials attesting the safety and security of these medications in reducing morbimortality in patients with AP.
Nutritional aspects

Patients with severe AP present a hypermetabolic and hyperdynamic state, also due to the magnitude of the systemic inflammatory response generated, which creates a highly catabolic state of organic stress.75

The studies about nutritional therapy in cases of AP are growing in number in recent years, and it has been the most discussed aspect in the management of patients with AP. Clinical practice, therefore, has changed a lot when compared to the last decades, when it was believed that absolute fasting was necessary to promote pancreatic recovery and, thus, reduce the stimulation of enzymatic secretion and the levels of inflammation of the gland. This traditional managing is associated with higher morbimortality and, usually, to a longer hospitalization of the patients.76

Better understanding of the effects of PN has led to more restricted indications of this modality in cases of AP. It has been demonstrated that PN impairs humoral and cellular immune responses, increases the magnitude of pro-inflammatory response, the bacterial translocation and the infection rates in experimental models and in patients with severe AP. On the other hand, the absence of enteral nutritional (EN) results in atrophy of the gastrointestinal mucosa, bacterial overgrowth, increased intestinal permeability and bacterial translocation. The early introduction of EN prevents mucosal atrophy and maintains the integrity of the intestinal mucosa and the associated lymphoid tissue; in addition, maintaining the normal intestinal bacterial flora, it limits the translocation of bacteria to the portal and systemic circulation and the consequent sepsis.77,78

Marik et al.79 reviewed, in meta-analysis, the main clinical trials comparing PN with EN and its respective outcomes in cases of patients with AP, in a total of nine clinical trials involving the adult population. The studied outcomes were mortality, rate of acquisition of new infections and organ failure and length of hospital stay. In almost all the studied outcomes in this meta-analysis, the EN was superior to the PN, with odds ratio of 0.5 for mortality (confidence interval of 95% – CI 95% 0.26 - 0.97), 0.33 for infections (CI 95% 0.2-0.54) and 0.32 for organic dysfunction (CI 95% 0.18-0.56). The very low risk of infection found in patients with EN may justify the reduction of mortality in the same group, considering the severity of the infection and sepsis as complicating factors in cases of AP. Olañá et al.80 updated the meta-analysis in 2010 including eight other clinical trials, finding large benefits in mortality reduction for patients receiving EN in most studies. Organic dysfunction was also studied by Wu et al.81 who found in a retrospective cohort study of 107 adult patients an incidence of organic dysfunctions four times higher in patients with prolonged PN when compared to those receiving EN.

Given the widespread acceptance of the EN benefits in patients with AP, the question was what should be the ideal enteral formulation for administration, considering the existence of more than 100 types of different formulations. Simply put, the formulas can be divided into three categories: elemental or semi-elemental, containing amino acids or oligopeptides, maltodextrins and medium and long-chain triglycerides; polymeric, containing no-hydrolyzed protein, maltodextrins and fructooligosaccharides, besides long-chain triglycerides; and the immunomodulatory diets, containing substrates that presumably modulate the activity of the immune system, such as probiotics, glutamine, arginine and omega-3 fatty-acids.82 In cases of AP, the use of elemental formulas presents a series of theoretical advantages when compared to polymeric formulas and, according to these theories, elemental formulas seem to be more advantageous and superior to polymeric in the initial nutritional therapy of AP, and they have better intestinal absorption, lower stimulus to pancreatic exocrine secretion and better tolerance; however, the significantly higher price of this type of elemental formulas and their reduced availability create a barrier for its widespread use.

Tolerance to enteral diet is also an obstacle to the progression of feeding and the consequent reduction of complications. Hegazi et al.83,84 retrospectively assessed adult patients with severe AP, classifying them in three groups according to the rate of progression of enteral feeding.

Petrov et al.84 studied clinical trials in meta-analysis comparing types of enteral formulations and the outcomes of patients with AP. The study analyzed 20 clinical trials and compared elemental diets with polymeric diets, diets with or without probiotics and diets with or without immunomodulators. Considering the outcomes – intolerance to diet, infection complications and mortality – there was no statistically significant difference between the types of diet studied.

Up to the present time, there are no clinical trials or reliable levels of evidence for recommendations only on diet in cases of AP in children; however, the early introduction of enteral diet is recommended within 48 hours, at most, after diagnosis, if the clinical conditions and the intestinal transit thus permit, reserving the option of PN only for patients with intolerance to the enteral nutrition, manifested by vomiting, abdominal distension and voluminous residues through the nasogastric or nasoenteral tubes.

Oral feeding should be preferred; however, if not possible due to the clinical condition, the diet should be administered via tube. Jejunal location is preferred so that the reduction in the pancreatic enzyme secretion is maximized;85 on the other hand, the exact placement of the tube in the jejunum requires endoscopy, a procedure that can bring risks to the child in severe condition, related to the procedure itself and to the need for sedation. The placement of a gastric tube is also possible, occurring migration to the first parts of the
Complications and prognosis of acute pancreatitis in children

The complications observed in children with AP can be immediate or late. Immediate complications may include hypovolemic and septic shock associated with dysfunction of multiple organs and systems. Renal dysfunction and cavity effusions, such as ascites and pleural effusion, as well as acute respiratory distress syndrome, may also complicate the patient's condition. The most common late complications include pancreatic necrosis and formation of pseudocysts. Pseudocysts, when poorly symptomatic and with no evidence of complications (such as infection and bleeding), may be managed without surgical intervention.

Mortality of children with AP may reach 11%, and higher rates are probably found in children with underlying diseases. This rate, lower than the one found for adults, may be explained by the near absence of cases of AP secondary to alcohol in children, an etiology with higher mortality. Many aspects, within the context of AP in children still need further clarification and specific prospective studies for evidence-based recommendations for this age group. As examples we can mention the validation of the diagnostic criteria used in adults, and the effectiveness of more sophisticated diagnostic methods, such as the IMR and the actual role of the ERCP as diagnostic and treatment.

Conclusion

AP is a disease of great importance in children, due to its difficult diagnosis and severity of symptoms and associated complications; besides, it has an increasingly higher incidence because of a growing suspicion and better knowledge of its clinical characteristics. The main causes of AP in children are biliary disease and medication, but up to 1/3 of patients may not have a defined etiology at diagnosis. Treatment relies on supportive measures and volume replacement in specific cases, as well as in the early introduction of EN, depending on the patient’s clinical conditions, in order to reduce morbidity associated with the disease. The early diagnosis and the proper management can contribute to better outcomes of patients and prevent immediate and late related complications.
Acute pancreatitis in pediatrics - Mekitarian Filho E et al.


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