SUMMARY OF THE DOCTORAL THESIS

GASTRITIS AND PEPTIC ULCER: CLINICAL AND ENDOSCOPIC ASPECTS, AND EVOLUTION IN CHILDREN

Doctoral supervisor,
Prof. BURLEA Marin, PhD.

Doctoral student,
IGNAT Ancuța

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INTRODUCTION

Pediatric gastroenterology evolved as a subspecialty of Pediatrics and Gastroenterology. The quick historical development of Pediatric Gastroenterology took place simultaneously in North America and Europe during the past four decades.

Endoscopy associated with endoscopic biopsies was a cornerstone for an accurate diagnosis, and currently it occupies a central place in Pediatric Gastroenterology (2).

In Romania, the first autonomous facility for Pediatric Gastroenterology was founded in Iași in 1995, in the "Sf. Maria" Emergency Clinical Hospital for Children.

In 1808, Broussais described the chronic gastritis as the most frequent and important disease. Thirty years later, his findings were supported by the changes noticed post-mortem (5).

As the morphological and topographical information became better known, different types and distribution patterns of gastritis were recognized and many classifications were designed.

In 1984, Warren and Marshall proposed as the etiology for the "idiopathic" chronic gastritis, the bacterial infection with Helicobacter pylori (H. pylori), thus revolutionizing the management of the gastroduodenal disease (7).

A few years later, the association between H. pylori and gastritis, peptic ulcer and gastric cancer became recognized and accepted with varying degrees of enthusiasm and a wide range of opinions with regard to its clinical implications (8). Shortly after the identification of the etiology of gastritis, effective therapies for the treatment of the infection with H. pylori were introduced.
The diagnosis of gastritis is a histological diagnosis achieved through random or targeted endoscopic biopsies. Numerous studies have reported *H. pylori* as the main etiological factor for moderate to severe gastritis (12).

In developed countries, the prevalence of the infection with *H. pylori* in children has been reported in <10%, and in children from the precarious social-economic environment the infection was reported in over 50% (16).

Mucosal lesions occur when causing agents, such as the gastric acid and nonsteroidal anti-inflammatory drugs (NSAIDs), exceed the mechanisms of mucosal defence.

The infection with *H. pylori* was associated with peptic ulcer, atrophy, intestinal metaplasia and gastric cancer (24).

Fig. 1.1 Schematic representation of the factors that contribute to the pathology of *H. pylori* infection in the stomach (27)

The diagnosis of chronic gastritis may be determined by histological examination. Therefore, the histological evaluation of
endoscopic biopsies is essential. Further laboratory tests could be necessary in order to identify the main cause of chronic gastritis and to evaluate the specific complications.

Testing for \textit{H. pylori} is used to diagnose the infection and to evaluate the efficacy of the therapy. There are several types of \textit{H. pylori} testing that may be conducted, both invasive and non-invasive.

Medical therapy is administered based on the cause and pathological findings. The goal of the therapy for the infection with \textit{H. pylori} is to obtain a rate of eradication of at least 90\% on the first attempt (94).

The prognosis of gastritis is closely tied to the underlying cause. The chronic gastritis associated with the infection with \textit{H. pylori} may evolve in some patients as an asymptomatic disease, while other patients may exhibit dyspeptic symptoms.

**EXTRADIGESTIVE MANIFESTATIONS OF THE INFECTION WITH \textit{H. PYLORI}**

In recent years, numerous studies have evoked the role of the infection with \textit{H. pylori} in a variety of extragastric events.

Table 1. VIII Extradigestive manifestations of the infection with \textit{H. pylori} in children (104)

<table>
<thead>
<tr>
<th>Extradigestive manifestations of the infection with \textit{H. pylori} reported in infants, children and adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron-deficiency anaemia</td>
</tr>
<tr>
<td>Immune thrombocytopenic purpura</td>
</tr>
<tr>
<td>Short stature</td>
</tr>
<tr>
<td>Low weight gain</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
<tr>
<td>Food allergy</td>
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<tr>
<td>Sudden infant death syndrome</td>
</tr>
</tbody>
</table>
Peptic ulcers represent discontinuities of the gastric or duodenal mucosa with the penetration of the mucosa muscle and the exposure of the sub-mucosa (125, 126).

The overall prevalence is estimated at 1.7% in the pediatric population and at 3.4 out of 10000 admissions (131).

A frequent cause of peptic ulcer in pediatric age is the infection with *H. pylori*, followed by the use of NSAIDs (128). Peptic ulcer also appears as a result of a stressful medical emergency or after surgery. It can occur as a result of severe burns (Curling ulcer) or as a result of severe head injuries (Cushing ulcer).

The initial therapy of the peptic ulcer in children is the medical one. The therapy of ulcers, as in the case of gastritis, includes the eradication of the infection with *H. pylori*. Surgical interventions are necessary in a small percentage of infants and in children with peptic ulcer complications (perforation, obstruction, intractable pain and bleeding that do not respond to medical or endoscopic therapy) (127).

As regards the ulcers caused by the ingestion of NSAIDS, the incidence of perforation is of approximately 0.3% per annum, and the incidence of obstruction is of approximately 0.1% per year (127). When the peptic ulcers cause is treated, the prognosis is excellent (148). The mortality rate for peptic ulcer is approximately 1 death out of 100000 cases. The death rate remains higher in infants, and also toddlers and young children with systemic diseases or acute bleeding or perforations (127).
CHAPTER 3
MOTIVATION AND OBJECTIVES OF THE DOCTORAL STUDY

Gastric pathology in children, primarily the gastritis and less the ulcers, is a topical theme, with plenty of controversy among researchers and clinicians, considering that the fast-food diet is more and more frequent among the young generations.

From the mastication deficiency, to the high intake of cholesterol and carbohydrates and low intake of vitamins and dietary fibres, all these contribute to imbalances such as constipation, obesity, and also gastritis and peptic ulcers.

The alert rhythm of our lives, the technology available from small ages, shortens the time for the approach of a healthy diet.

The characteristic pathology of the adult is seen increasingly more frequently in children; the aggressive therapy of these illnesses, the glucocorticoids, new strains of viruses and bacteria and their resistance to antibiotics, all these contribute to the onset of gastritis and peptic ulcers.

The existence of these factors led me to choose this topic for my doctoral thesis, being convinced that this pathology is not only topical, but it will remain also a pathology of the future that will be increasingly more difficult to control using the current therapy.

Considering the characteristics of growth and development in children, it is expected that some clinical, endoscopic, histological and bacteriological features, and also the complications and therapy of the illness have certain shades that customize this pathology in comparison to the same pathology in adults.

Furthermore, the possible proximity esophageal and duodenal suffering, malnutrition or obesity, extradigestive manifestations of the infection with *H. pylori*, as well as the
associated pathology, may transform the clinical and evolotional aspects of the illness, bringing out diagnostic difficulties and requesting different therapeutic attitudes.

From these premises, the paper proposes the following objectives:

- evaluation of the distribution of cases according to sex, age, origin environment with a view to the discovery of certain particulars relating to these parameters for both gastritis and the peptic ulcers;
- quantification and comparison of the diagnostic methods available and the setting of a protocol for the investigation of gastric diseases in order to obtain accurate data for our region;
- analysis of the different types of gastritis and peptic ulcers and the secondary diagnosis associated endoscopically;
- the study and development of correlations between the clinical aspects (specific and nonspecific) and the infection with *H. pylori*;
- studying of both digestive and extradigestive involvement of the infection with *H. pylori*;
- establishing the treatment schemes according to the etiopathogenesis of the disease, the modification of clinical parameters, the persistence of endoscopic aspects and the rate of relapse of the condition;
- evaluation of the complications of the disease and the evolutionary particularities;
- comparing the results with data from the literature.
A retrospective study was conducted over a period of 3 years (01.04.2013-31.03.2016), on a group of 1757 patients of both sexes, aged between 0 and 18 years, hospitalized mostly in the 5th Clinic of Pediatric Gastroenterology as well as in other clinics of the "Sf. Maria" Emergency Hospital for Children, Iasi, with suggestive manifestations of peptic ulcer or gastritis, subjected to digestive endoscopy.

The main criterion for inclusion in this study was the definite diagnosis of this condition by performing UGI endoscopy with biopsies taken from the gastric and/or duodenal mucosa.

During this period, 2042 UGI endoscopies have been carried out, of which we excluded 256 of UGI endoscopies performed to verify the response to therapy and not for initial diagnosis. From the 1786 children who were submitted to UGI endoscopy for diagnostic purposes, 29 children were also excluded, as we did not have their complete personal data. The final number of children on which the study was conducted was 1757.

The research was based on accumulating data from the patients’ consultation charts and the discharge notes in the database of the hospital. We also used the results of endoscopies and the laboratory results for *H. pylori* antigen in stool samples.

Digestive endoscopy and taking biopsies are fundamental for the diagnosis and management of digestive diseases. This allows the direct visualization of the mucosa of the esophagus, stomach and proximal duodenum. The correct sampling of biopsies is necessary for an accurate diagnosis.

Such data have been processed using the SPSS 17.0 platform and excel 2016.
GASTRITIS

Demographic results
The 1757 children diagnosed with gastritis and/or peptic ulcer were unevenly distributed depending on the month of admission, with a higher prevalence in the months of February-March and October-November.

In the studied lot, the female patients accounted for about two-thirds of the entire lot with a percentage of 68.92%. The distribution of cases depending on the environment of their origin showed a higher frequency of children from the rural area with a rate of 63.35%. The presence of gastric pathology was more common in adolescents. The highest frequency was recorded at the age of 16 with 272 cases out of 1757 patients (15.5%). This disorder affects also very young children, the lowest frequency being at the age of 1 year, with 4 cases.

The average age of children in the study group was 13.18 years, with a standard deviation of 3.504 SD. Statistical analysis showed a lower average age of diagnosis of gastric pathology in the urban environment.

Digestive manifestations of the infection with *H. pylori*
From the 1757 children diagnosed with different forms of gastritis and peptic ulcers, in 542 (30.85%) the disease was associated with *H. pylori* infection.

- **Comparison of the methods for the diagnosis of the infection with *H. pylori***
  From 574 children whose infection with *H. pylori* was diagnosed after the urease test, in 541 children (94.25%), the
infection was confirmed by direct microscopic examination. From the statistical analysis it was observed that there is a very significant difference between the two powerful methods for identifying the infection with *H. pylori* ($\chi^2; p<0.001$). Referring to the results obtained through microscopic examination, the urease test had very good sensitivity (Sn = 99.81%) and specificity (Sp = 97.28%) values. The dosing of the *H. pylori* Ag in stool has acceptable sensitivity (Sn=82.60%) and specificity (Sp=89.28%) values.

- **Demographic results in the infection with *H. pylori***
  
  In the studied group, the average age of the children infected with *H. pylori* was higher (14.10 ± 2.833 SD) compared to the children without *H. pylori* (12.78 ± 3.694 SD), the average difference being of 1.3 years.

  The distribution of the children infected with *H. pylori*, according to gender, showed a frequency of 26.75% in boys and a frequency of 73.25% in girls.

  The distribution of the children infected with *H. pylori*, according to the origin environment, showed a frequency of 24.72% in rural areas and a frequency of 75.28% in urban areas.

  The main types of gastritis diagnosed by upper gastrointestinal endoscopy, in the order of frequency, were represented by: purpura gastritis (44.28%), purpura - nodular gastritis - 22.65%), diffuse gastritis (12.35%), nodular-antral gastritis (8.99%), hemorrhagic erosive gastritis - (4.38%), hypertrophic gastritis (4.15%), erosive gastritis (1.99%), haemorrhagic gastritis (0.46%), nodular-aphthous gastritis (0.46%) and atrophic gastritis (0.29%). Analysing the distribution of the various types of gastritis according to the presence of the infection with *H. pylori*, it was noticed that it was more common in the forms of nodular (antral-nodular, purpura-nodular and nodular-aphthous) gastritis.
The association between gastritis and gastroesophageal reflux disease

Of the 1757 children diagnosed with gastritis, the gastroesophageal reflux disease was present in 1017 patients (57.88%).

Of the 542 patients with gastritis with *H. pylori*, 315 also had GERD. The statistical analysis did not reveal a significant difference of the association between the infection with *H. pylori* and GERD ($\chi^2; p > 0.05$).

Secondary diagnoses of gastritis revealed by upper gastrointestinal endoscopy

In addition to the main diagnosis of gastritis and peptic ulcer (analysed in a separate chapter) UGI endoscopy also objectified various forms of duodenitis, varying degrees and forms of esophagitis, foreign bodies that have required endoscopic extraction, upper digestive hemorrhage, polyps with different locations (esophageal, gastric or duodenal), gastroesophageal reflux, esophageal stenosis, esophageal varices. The most common
pathologies associated to gastritis in children were duodenitis with 1338 cases (76.1%) and esophagitis with 1017 cases (57.8%).

**Gastritis symptoms in children**

The main symptoms that led to hospitalization in the Pediatric Gastroenterology Clinic and which resulted in the diagnosis of gastritis were represented, in order of frequency, by: abdominal pain in 1664 cases (94.7%), nausea in 668 cases (38.0%), vomiting in 468 cases (27.2%), loss of appetite in 243 cases (13.8%), heartburn in 144 cases (8.2%), headache in 130 cases (7.4%), vertigo in 87 cases (5.0%), constipation in 57 cases (2%), flatulence in 56 cases (6.2%), asthenia in 26 cases (1.5%) and early satiety in 17 cases (1.0%).

**Treatments used in the history of children with gastritis**

There were cases in which patients diagnosed with gastritis had received for other pathologies different treatments which may have influenced the emergence of the gastric pathology. Thus, 105 children (6.0%) had been treated with NSAIDS, 78 children (4.4%) had been treated with corticosteroids, 170 children (9%) had been treated with recurrent antibiotics, and 146 children (8.3%) had received other treatments.

**Extradigestive manifestations of the infection with H. pylori**

Knowing the involvement of *H. pylori* in extradigestive manifestations, we analysed statistically all the possible associations between the infection with *H. pylori* and the encountered pathologies. From the statistical analysis it was observed that there is a very strong association of the bacterial infection with iron deficiency anaemia ($\chi^2$; p<0.001), ponderal hypotrophy ($\chi^2$; p<0.01), the hepatic cytolysis syndrome ($\chi^2$; p<0.01), respiratory diseases ($\chi^2$; p<0.05) and acute dehydration syndrome ($\chi^2$; p<0.05).
Ultrasound changes

Of the 1757 children, 988 (56.23%) were submitted to abdominal ultrasound. Among those who were subjected to abdominal ultrasound, changes in the studied pathology were represented by cholecystopathy (calculous or non-calculous cholecystitis, septate cholecyst, hypotonic cholecyst) to an extent of 10.1% (177 cases), gastric stasis in a percentage of 20.0% (352 cases), duodenal stasis in a percentage of 8.1 (142 cases), aerocoly in a proportion of 9.2% (161 cases) and hepatic steatosis in a percentage of 3.4% (60 cases).

Histopathological examination of biopsy samples collected through UGI endoscopy

Referring the presence of *H. pylori* + to the microscopic exam results on the smear, the sensitivity was 47.22% and the specificity of 97.08%. Referring the presence of *H. pylori* + + to the microscopic exam results on the smear, the sensitivity was 20.45% and the specificity of 100%.

From the statistical analysis, the association between the lymphoid nodules described in the histopathological examination of the biopsies sampled from the gastric mucosa and the presence of the infection with *H. pylori* was not significant ($\chi^2$; p>0.05).

PEPTIC ULCERS

Demographic results

From the 1757 children participating in the study, the newly-diagnosed peptic ulcer was present in 32 cases (1.82%). 17 of the 32 patients had stomach ulcer and 15 had duodenal ulcer.

By analysing the seasonal incidence of peptic ulcers, it was observed that the ulcer maintains the same seasonal distribution as gastritis, most of the cases being recorded in the months of February-March and October-November.

Analysing the distribution of the patients depending on the gender variable, we obtained an equal distribution, 16 male
patients (50% of the cases) and 16 female patients (50% of the cases).

By analysing the distribution of peptic ulcer considering the origin environment variable, there was a higher frequency of children with peptic ulcer in the rural areas, with a rate of 68.75%.

The average age of diagnosis of the peptic ulcer in children was $13.19 \pm 3.477$ SD. Statistical analysis showed a lower value of the average age of diagnosis of the peptic ulcer in urban areas ($12.20 \pm 5.095$ SD), compared to the rural ones ($13.64 \pm 2.460$ SD), but without statistical significance.

**Peptic ulcer symptoms in children**

Abdominal pain was the main symptom for which patients with peptic ulcers were hospitalized in the Gastroenterology Clinic, in 87.5% of the cases.

**Treatments used in the history of children with peptic ulcers**

Similarly to gastritis, there were cases in which patients diagnosed with peptic ulcers had received for other pathologies different treatments which may have influenced the emergence of gastric pathology. There were 2 cases of NSAID post-administration ulcers.

**Peptic ulcer and the infection with $H. pylori$**

Of the 17 cases of gastric ulcer, in 5 cases (29.41%) the infection with $H. pylori$ was present. In the case of duodenal ulcer, bacterial infection was present in 12 of 15 children (80%).

**Complications of peptic ulcer in children**

Of the 32 peptic ulcer cases, 4 also suffered from the complication of upper digestive hemorrhage, and the children were admitted to hospital with blood vomiting or hematemesis. None of the 4 gastric ulcers was associated to the infection with $H. pylori$. During the 3 years of study, there were no perforated ulcer cases.
TREATMENT OF PEPTIC ULCERS AND GASTRITIS

Treatment schemes in the infection with \textit{H. pylori}

The most common treatment scheme for gastritis and peptic ulcers in children was based on amoxicillin + clarithromycin + proton pump inhibitor. It was used in 539 cases. In terms of frequency, amoxicillin + ciprofloxacin + proton pump inhibitor was the second scheme (24 cases), the third and last scheme being composed of clarithromycin + metronidazole + proton pump inhibitor (4 cases).

Treatment with proton pump inhibitors

1753 of the 1757 children were treated with PPI. PPIs used as single therapy, in combination with other symptomatic therapies or in the therapy schemes for the eradication of the infection with \textit{H. pylori} were represented by esomeprazole in 846 cases (48.2%), pantoprazole in 883 cases (50.3%) and omeprazole in 24 cases (1.4%).

Analysing the management of inhibitors during the 3 years of study, it was observed that the main PPIs used in Pediatrics were pantoprazole and esomeprazole.

Other treatments used in gastric pathology

In addition to the treatment schemes for the eradication of the infection with \textit{H. pylori} and PPI, in some cases patients received other symptomatic treatments. The most common symptomatic treatments were represented by trimebutine in 582 cases (33.1% of patients received this treatment), domperidone in 485 cases (27.6% of patients), antacids in 484 cases (27.5% of patients), and last in frequency are the antimycotics in 3 cases (0.2% of patients) and bismuth in one case (0.1%).
GASTRITIS

In our study, analysing the seasonal distribution of children with various types of gastritis, a rise in frequency was noticed in the second half of autumn (October-November) and during the winter-spring months (February-March). Living standards, seasonal diets lacking fresh fruit and vegetables, especially in winter, vitamin deficiencies, and common childhood infections may affect this seasonal distribution.

In Romania, the authors of a retrospective study conducted in Cluj Napoca, on 194 children, reported the overall prevalence of the infection with \(H. pylori\) as being 36.6% (18). In our study, we obtained a prevalence of the infection with \(H. pylori\) of 30.85%, similar to that reported in the studies from Romania.

The average age of diagnosis of the infection with \(H. pylori\) was 14.10 ± 2.833SD, higher than the one reported in Târgu Mureș (12.9) (166). An increase in the prevalence of the infection with \(H. pylori\) with age, regardless of the economic status of the country has been observed in several studies from around the world. The predominance of the infection with \(H. pylori\) in girls could be explained by the higher addressability to the physician, and through a greater reactivity to this category.

The bile reflux is one of the main factors involved in the pathophysiological processes that causes lesions of gastric mucosa in patients with chronic gastritis. Duodenogastric reflux becomes pathological when it is excessive or when it lasts for a long time (176, 177). The relationship between gastritis caused by \(H. pylori\) and GERD was controversial in the medical literature of the past decade (180).
Headache is commonly reported by patients with various gastrointestinal symptoms (198, 199). However, in recent years, research has focused on the role of the *H. pylori* infection in the pathogenesis of the migraine. It is postulated that the recurring headache secondary to the infection with *H. pylori* may be a result of the vasospastic systemic effects of the proinflammatory substances released by the infected gastric mucosa (200).

NSAID are considered to be safe drugs for the control of the fever. Contrary to their benefits, there is evidence that demonstrates that their side effects include gastritis, peptic ulcer, digestive hemorrhage and perforation (206).

The infection with *H. pylori* has been associated with various extra-gastric disorders, such as: iron deficiency anaemia, chronic idiopathic trombocytopenic purpura, delay in growth and diabetes (200, 209).

**PEPTIC ULCERS**

Peptic ulcers represent a relatively rare phenomenon in children. Peptic ulcers are usually secondary to systemic diseases or drugs in young children, without recurrences. In contrast, duodenal ulcer in older children and adolescents show relapses and it is known to be linked to the coexistence of the chronic active antral gastritis and of the infection with *H. pylori* (242).

By analysing the seasonal incidence of the peptic ulcer, it is noted that the ulcer maintains the same seasonal distribution as gastritis.

The international literature reports a dominance of young boys associated to peptic ulcer (252).

In a multicentre study in Europe, where the frequency of digestive endoscopy in children was examined, the symptoms the most often reported were epigastric sensitivity, when the child wakes up during sleep, hematemesis, melena and stagnant weight (254).

The authors of a study reported *H. pylori*-positive gastric ulcer in 23 of 27 children (85.2%) and *H. pylori*-positive duodenal
ulcer in 10 of 13 children (76.9%). Of the 7 children with both gastric and duodenal ulcers, 5 (71.4%) were also infected with *H. pylori* (245).

Peptic ulcer remains a disease with high morbidity and mortality, despite the availability of effective antacid medications. The main complications of peptic ulcer are perforation, bleeding and obstruction. The introduction of therapies for the eradication of the infection with *H. pylori* and antacid drugs have reduced the need for the elective surgery, but the surgery of acute complications was not reduced (130). The perforation of the peptic ulcers occurs in 10% of the cases of ulcers in adults and in 12.5% of the cases in children (255, 252).

**TREATMENT OF PEPTIC ULCERS AND GASTRITIS**

The infection with *H. pylori* in young children and adolescents is a chronic, persistent infection that causes chronic gastritis, atrophic gastritis, intestinal metaplasia and gastric adenocarcinoma (259, 260). Therefore, the eradication of the infection with *H. pylori* is required to decrease the risk of developing gastric cancer (261, 262). The resistance to antibiotics is the main cause of failure when treating the infection with *H. pylori* (263).

The treatment with PPI in peptic disease has increased dramatically over the last 3 decades in patients of all ages (278). PPIs have gained popularity for the acid suppression since they inhibit the last stage of the gastric acid secretion, irrespective of the acid secretion stimulant and that can be given once a day to most patients (279).

The long-term inhibition of gastric acid secretion by the use of PPI leads to hypergastrinemia, hyperplasia of enterochromaffin-like cells, vitamin B12 deficiency, hypomagnesaemia, necrotizing enterocolitis, osteoporosis, atrophic gastritis, and increased frequency of infections (295).
CONCLUSIONS OF THE THESIS

The most important cause of the studied pathology is the infection with *H. pylori*, and in infants, the use of NSAIDS is important not regarding the frequency, but regarding the amplitude of lesions that can occur from age-appropriate doses. To identify the infection with *H. pylori*, the endoscopy with sampled biopsies followed by the urease test and/or direct microscopy remains the gold standard.

The relationship between nodular gastritis and the infection with *H. pylori* remains unclear. Although the association between *H. pylori* and two types of nodular gastritis (antral-nodular and purpura-nodular) was statistically significant, however, the sensitivity and specificity values obtained in our study were not very good.

We can support neither the protective role of the infection with *H. pylori* as it has been suggested by some authors, neither the fact that the infection with *H. pylori* itself determines the appearance of the GBR, therefore further studies are needed to establish a possible association.

Although we have obtained statistically significant associations between different clinical manifestations and the infection with *H. pylori*, we cannot affirm that the infection with *H. pylori* itself determines the presence of abdominal pain and vomiting, this symptomatology can be present also in gastritis without infection with *H. pylori*, and also in the duodenitis associated to gastritis.

The statistical analysis revealed a significant association between the infection with *H. pylori* and the iron deficiency anaemia, ponderal (not height) hypotrophy, hepatic cytolysis syndrome, respiratory diseases and acute dehydration syndrome.


