

## Neuro-gastroenterology and Motility Disorders

Paolo Quitadamo MD, Efstratios Saliakellis MD PhD, Osvaldo Borrelli MD PhD and Nikhil Thapar BM PhD\*

Division of Neurogastroenterology and Motility, Department of Paediatric Gastroenterology, UCL Institute of Child Health and Great Ormond Street Hospital, London, UK.

\*Corresponding author:

Dr. Nikhil Thapar BM MRCPCH PhD

Division of Neurogastroenterology and Motility

Department of Paediatric Gastroenterology

UCL Institute of Child Health and Great Ormond Street Hospital

30 Guilford Street

London

United Kingdom

WC1N 1EH

Email: [n.thapar@ucl.ac.uk](mailto:n.thapar@ucl.ac.uk)

Fax: + 44 20 7813 8382

Gut Motility disorders comprise a heterogeneous group of disorders that result from disruption of the functional integrity of the intrinsic neuromusculature of the gastrointestinal (GI) tract. This intrinsic neuromusculature includes the smooth muscle layers, the intrinsic nervous system of the GI tract (enteric nervous system or ENS) and the interstitial cells of Cajal. The contribution of each of these components to function can be compromised by alterations in structure (ranging from absence to derangement in numbers and/or anatomy) or of function (complete or partial failure in physiological function). This pathology can be primary or secondary to a number of insults e.g. infections, inflammation, toxins etc. In children disorders may be congenital being present from birth or acquired later in life. Finally involvement of the enteric neuromusculature can be patchy/segmental or affect the gastrointestinal tract diffusely.

Neuro-gastroenterology is the study of the interface of all aspects of the gastrointestinal tract or digestive system with the different branches of the body's nervous system including the enteric, central and autonomic nervous systems. The combined terms 'Neurogastroenterology and motility' are designed to encompass the study of all the components of the enteric neuromusculature and their modulating influences and represents one of the fastest growing areas in gastroenterology clinical practice and research. This chapter aims to address some of the most common neurogastroenterology and motility conditions seen in clinical practice ranging from those with defined pathology to those which fall under the umbrella of functional gastrointestinal disorders. The latter comprise some of the commonest but challenging disorders and the term 'functional' reflects the fact that in the majority of such conditions no organic cause can be found. It should also be noted that at the present time many functional disorders e.g. abdominal pain-related functional GI disorders, represent symptom complexes that can further be subdivided into more discrete entities e.g. irritable bowel syndrome, functional abdominal pain etc depending on the nature, location and associations of the symptoms. Clinicians will often rely on the presence or absence of 'red flags' e.g. associated weight loss, severe or significant symptoms etc to decide whether patients are likely to have organic or functional disorders. Exhaustive investigations in the latter are likely to prove fruitless, expensive and perpetuate 'illness behaviours' in the patients.

## **Abdominal pain-related functional gastrointestinal disorders**

### ***Introduction***

Abdominal pain-related functional gastrointestinal disorders (FGID) constitute a spectrum of conditions characterised by the presence of recurrent abdominal pain in the absence of any defined pathology <sup>1</sup>. In the past these disorders fell under the single term 'Recurrent abdominal pain' (RAP) but have since been re-categorised under an international initiative (Rome Foundation) to improve the diagnosis and classification of such conditions. The Rome III criteria <sup>2,3</sup> are currently being utilised (summarised in Tables 1-5).

RAP is frequently encountered as a presenting complaint in pediatrics <sup>4,5</sup>. In the majority of patients no organic disease is identified <sup>6</sup>. Despite its benign nature the persistence of symptoms can result in significant stress to children and their families as well as clinicians concerned at the possibility of missing an underlying pathology. With the implementation of the Rome III criteria, abdominal pain-related FGID, have been framed as a positive diagnosis rather than one of exclusion <sup>3</sup>, which will hopefully facilitate the reduction of unnecessary diagnostic procedures and expedite the initiation of appropriate treatment <sup>7</sup>.

### ***Epidemiology***

The prevalence of childhood abdominal pain-related FGID in western countries has been estimated to be between 0.3 to 19% <sup>8</sup>. Various definitions and diagnostic criteria used for such disorders prior to the development of the ROME III criteria are likely to have accounted for the wide range of the reported prevalence.

### ***Pathophysiology***

The pathophysiological model for abdominal pain-related FGIDs is undoubtedly multifactorial <sup>9</sup>. It has been proposed that various mechanisms such as genetics, early life events, environmental, gastrointestinal and

psychosocial factors act together in a complex interplay ultimately resulting in an alteration to the gut-brain axis<sup>10,11,12,13,14,15,16</sup>. Afferent signals from the gastrointestinal tract transmitted via the pain pathways are subsequently amplified and the patient's perception of painful stimuli is in turn enhanced<sup>17</sup>. These phenomena have been defined as visceral hypersensitivity and central hypervigilance respectively<sup>14</sup>.

### ***Clinical presentation***

According to Rome III criteria abdominal pain-related FGIDs can be classified into the following five categories: Functional Abdominal Pain (FAP), FAP syndrome, functional dyspepsia, abdominal migraine and irritable bowel syndrome (IBS).

Tables 1-5. Rome III diagnostic criteria for abdominal pain-related FGID (adapted from Rasquin A. *et al.*<sup>3</sup>).

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Table 1. Diagnostic criteria for FAP in children

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All of the following criteria must be present at least once a week for a period of  $\geq 2$  months prior to the diagnosis:

1. Abdominal pain (intermittent or continuous)
  2. Criteria insufficient for the diagnosis of other abdominal pain-related FGID
  3. Absence of evidence of possible organic disease that could account for patient's symptomatology
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Table 2. Diagnostic criteria for FAP Syndrome in children

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FAP must be present at least 25% of the time plus  $\geq 1$  of the following:

1. Some loss of functioning on a daily basis
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2. Presence of somatic symptoms (e.g. headache, sleeping difficulties, limb pain)

The above criteria must be present at least once a week for a period of  $\geq 2$  months prior to the diagnosis.

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Table 3. Diagnostic criteria for functional dyspepsia in children

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All of the following criteria must be present at least once a week for a period of  $\geq 2$  months prior to diagnosis:

1. Presence of pain (persistent or recurrent) or discomfort localised in the upper abdomen (above the level of umbilicus)
  2. Criteria insufficient for the diagnosis of IBS
  3. Absence of evidence of possible organic disease that could account for patient's symptomatology
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Table 4. Diagnostic criteria for abdominal migraine in children

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All of the following criteria must be present at least once a week for a period of  $\geq 2$  months prior to diagnosis:

1. Paroxysms of intense and acute periumbilical pain (duration  $\geq 1$  hour)
  2. Intervals of usual health (duration: weeks to months) between the episodes of pain
  3. The pain affects child's normal activities
  4. The pain is associated with  $\geq 2$  of the following:
    - a. Anorexia
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b. Nausea

c. Vomiting

d. Headache

e. Photophobia

f. Pallor

4. Absence of evidence of possible organic disease that could account for patient's symptomatology

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Table 5. Diagnostic criteria for IBS in children

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1. Abdominal discomfort or pain associated with  $\geq 2$  of the following at least 25% of the time:

a. Improvement with defecation

b. Onset of pain associated with a change in the frequency of bowel motions

c. Onset of pain associated with a change in the consistency (form) of stools

2. Absence of evidence of possible organic disease that could account for patient's symptomatology

The above criteria must be present at least once a week for a period of  $\geq 2$  months prior to the diagnosis.

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During history taking, physical examination and interpretation of first-line blood tests, there are certain features that may suggest the presence of an underlying organic pathology. Physicians need to be aware of these "red-flag" signs/symptoms, which are summarised in Table 6 <sup>1</sup>.

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Table 6. 'Red flag' or alarm features that may suggest the presence of an underlying organic pathology for

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recurrent abdominal pain in children

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From history

Onset of symptoms <5 years of age

Presence of constitutional symptoms (eg fever, weight loss)

Presence of nocturnal symptoms (eg pain that awakens the child, diarrhea)

Gastrointestinal bleeding

Vomiting

Dysphagia

Persistent right upper or lower abdominal quadrant pain

Presence of referred pain (back, shoulders, extremities)

Dysuric symptoms

Family history of inflammatory bowel disease, celiac or peptic ulcer disease

From physical examination

Faltering growth, delayed puberty

Hepato-splenomegaly

Jaundice

Signs of perianal disease (tags, fissures, fistulas)

From first-line blood test

Anaemia, neutropenia or thrombocytopenia

Hypoalbuminemia

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Elevated inflammatory markers (white blood cell count, erythrocyte sedimentation rate, C-reactive protein)

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The identification of alarm features should guide the diagnostic procedure towards excluding an organic disease. Amongst the myriad of pathologies that could potentially present with abdominal pain Table 7. below lists those most frequently encountered in pediatrics.

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Table 7. Potential organic disorders as differential diagnoses of recurrent abdominal pain

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### **Gastrointestinal system**

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Gastroesophageal reflux

Peptic ulcer disease

Coeliac disease

Eosinophilic gastrointestinal disease

Food allergy

Inflammatory bowel disease

Chronic constipation

Malrotation

Hernias

Intussusception

Tumors (eg lymphoma)

### **Pancreatic and hepatobiliary**

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Cholelithiasis

Cholecystitis

Chronic hepatitis

Chronic pancreatitis

**Respiratory system**

Pneumonia

**Genitourinary system**

Nephrolithiasis

Pyelonephritis/Cystitis

Ureteropelvic junction obstruction

Hematocolpos

**Musculoskeletal system**

Trauma

Tumors

**Other systems**

Sickle cell disease

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Leukemia

Diabetes mellitus

Porphyria

Familial mediterranean fever

Lead poisoning

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### ***Diagnostic investigations***

Laboratory tests, imaging studies and endoscopic procedures should be performed wisely and guided by the information obtained from the history and physical examination. Although there is lack of evidence to evaluate the usefulness of blood tests as a discriminatory tool between functional and organic disease, a limited number of first line tests may be warranted. It has been proposed that these should include a full blood count with differential, erythrocyte sedimentation rate, C-reactive protein, coeliac serology, urinalysis, urine culture, and faecal examination for ova and parasites<sup>18,19</sup>. Extensive diagnostic investigations should be avoided as they are usually not clinically indicated, are of significant financial cost and ultimately impair the physician-patient relationship as they increase patient's uncertainty regarding the diagnosis and the overall treatment plan<sup>1</sup>.

### ***Treatment***

The management plan of the childhood FAP should be based on the biopsychosocial model for FGID and needs to incorporate a multidisciplinary approach specifically developed to each child's symptomatology and identifiable triggers<sup>17</sup>.

Dietary interventions (such as food elimination diets) and use of probiotics have shown favourable results in certain groups of patients with FAP, however more data are needed in order to fully evaluate their therapeutic efficacy<sup>20,21</sup>.

Psychosocial interventions (eg parental education, family therapy, relaxation, distraction, hypnotherapy, biofeedback) are also very effective in reducing the severity and maintenance of somatic symptoms in children with abdominal pain-related FGID<sup>22</sup>. Indeed it has been shown that hypnotherapy in particular is a highly beneficial therapeutic modality even when compared to conventional medical care resulting in long-term remission in children with either FAP or IBS<sup>23,24</sup>. More work needs to address the modalities and resources needed to deliver hypnotherapy in the broader clinical arena.

Certain groups of drugs such as antidepressants (eg tricyclic antidepressants, serotonin reuptake inhibitors), antispasmodics (eg peppermint oil, hyoscyamine), cyproheptadine and prokinetics (eg domperidone, erythromycin) have been reported to be successful in the treatment of childhood FAP and are used widely, albeit variably<sup>25,26,27,28,29</sup>. There is, however, a clear lack of well-controlled trials to precisely support the efficacy long-term of the aforementioned medications in the pediatric population. Thus the benefit of their use in clinical practice is yet to be elucidated<sup>30</sup>. With regard to complementary and alternative medicine (herbal preparations, acupuncture) there are currently no sufficient data to support their potential therapeutic role in childhood FAP<sup>18,31</sup>.

Overall, robust randomised placebo-controlled trials are needed to assess these agents especially given reports of substantial placebo effects of up to 50%<sup>32</sup>.

### ***Prognosis***

Long-term follow-up of children with RAP reveals that 35-50% of them will eventually progress to complete resolution of their symptoms, whereas at least 25% will continue to experience abdominal pain in adulthood. Amongst children with RAP those who had been given a clear and simple explanation of their condition

along with the physician's reassurance were less likely to express extra-abdominal complaints or relapse later in life<sup>33,34,35</sup>. Male gender, onset of symptoms at an age younger than 6 years, duration of symptoms >6 months, low educational and socioeconomic status, presence of a so-called 'painful family' and an increased number of surgical procedures (eg tonsillectomy, appendectomy) have been established as poor prognostic indicators for the long-term outcome of children with RAP<sup>33,35</sup>.

### ***Conclusions***

Abdominal pain-related FGIDs may result in a significant impairment of the well being of children and their families as well. The role of the physician is crucial in advising the family to adopt appropriate parenting styles, which create a supportive and loving environment that subsequently reduces the anxiety caused in children by minor injuries/illnesses and other stressful situations that they may encounter.

The diagnostic approach and therapeutic management of a child presenting with RAP may be challenging. A detailed history combined with a thorough clinical examination as suggested by the Rome III criteria remains the cornerstone for diagnosis. Baseline laboratory investigations may aid the establishment of a positive diagnosis of FGID, thereby leading to prompt appropriate management and better long-term outcomes.

## **Functional Constipation**

### ***Introduction***

Chronic constipation is a common problem in children with a reported prevalence of between 0.7% and 29.6% (median 12%)<sup>36</sup>. Most often it is defined as a delay or difficulty in defecation present for at least 2 weeks sufficient to cause significant distress to the patient<sup>37</sup>. A normal pattern of stool evacuation is commonly thought to be a sign of health in children of all ages. Especially during the first months of life, parents pay close attention to the frequency and the characteristics of their babies' defecation. Any deviation from what they thought to be normal may trigger a call to the nurse or a visit to the pediatrician. Thus, it is not surprising that approximately 3% of general pediatric outpatient visits and 25% of pediatric gastroenterology consultations are related to a perceived defecation disorder<sup>38</sup>. Chronic constipation is an important source of anxiety for parents who often worry that a serious disease is causing the symptom, accepting that beyond the neonatal period, the most common cause of constipation in children is functional with only a small minority of children thought to have an organic cause.

### ***Pathophysiology***

Functional constipation is defined as constipation without objective evidence of a pathological condition and is thought to result from painful bowel movements with consequent voluntary withholding of feces by a child who wants to avoid unpleasant defecation. Several events can lead to painful defecation such as toilet training, changes in routine or diet, stressful events, intercurrent illness, deliberate avoidance or unavailability of toilets e.g. at school, or the child's postponing defecation because he or she is too busy. Withholding feces can lead to protracted fecal stasis in the colon with resorption of fluids leading to both a change in stool consistency and an increase in their overall size. The passage of large, hard stools that painfully stretch the anus may frighten the child and result in a fearful determination to avoid all defecation. Such children respond to the urge to defecate by contracting their anal sphincter and gluteal muscles, attempting to withhold stool<sup>39,40</sup>. Eventually, the rectum habituates to the stimulus of the enlarging fecal mass, and the urge to defecate slackens. After a while, such retentive behavior becomes an automatic

reaction. As the rectal wall stretches, fecal soiling may occur, angering the parents and frightening the child<sup>41</sup>. After several days without a bowel movement, irritability, abdominal distension, cramps, and decreased oral intake may appear.

### ***Diagnosis***

Currently, the most widely accepted criteria to diagnose childhood functional constipation are the Rome III criteria (Table 1)<sup>2,3</sup>. There are 2 sets of criteria based on the age of the patient (i.e. below and above the age of 4 years) and the diagnosis is based on careful clinical history and examination. The history should include both a personal (e.g. age at first passage of meconium and onset of symptoms, acquisition of developmental milestones and growth parameters, associated symptoms including bilious vomiting or rectal bleeding etc) as well as family history (e.g. gastrointestinal disease, allergy, other non-gastrointestinal disorders etc). Examination should focus on general well-being, growth parameters, the abdomen for organomegaly, distention and masses, inspection of the anus, as well as examination of the lumbosacral spine and neurology. Table 2 lists a number of 'red flags' that should alert the clinician to the possibility of organic disease underlying the constipation. The presence of one or more of these should raise the suspicion for organic cause of constipation and need for further workup. It should be noted that this list is not exhaustive.

**Table 1. Rome III criteria for children aged below and above 4 years (adapted from references<sup>2,3</sup>)**

<b>Rome III diagnostic criteria for functional constipation in children up to 4 years of age *</b>
Two or fewer defecations per week
At least one episode/week of incontinence after the acquisition of toileting skills
History of excessive stool retention
History of painful or hard bowel movements
Presence of a large fecal mass in the rectum
History of large diameter stools which may obstruct the toilet
* must include one month of <i>at least 2</i> of the following

<b>Rome III diagnostic criteria for functional constipation in children older than 4 years of age *</b>
1. Must include <i>two or more</i> of the following:
- Straining during at least 25% of defecations
- Lumpy or hard stools in at least 25% of defecations
- Sensation of incomplete evacuation for at least 25% of defecations
- Sensation of anorectal obstruction/blockage for at least 25% of defecations
- Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
- Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome
*criteria fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis

**Table 2. Red flags**

<b>Main red flags for organic constipation</b>
Delayed passage of meconium after birth (> 48 hours)
Early onset (first months of life)
Family history of Hirschsprung disease
Growth failure
Abnormal examination of lumbosacral spine (sacral dimple, patch of hair, gluteal cleft deviation)
Abnormal neurological examination of anal reflexes and/or lower limbs
Abnormal anus (position, scars, fistulae)
Other significant signs or symptoms (blood in stools in the absence of visible anal fissures, massive abdominal distention, bilious vomiting, fever)
Unusual history and examination findings (consistent empty rectal ampulla on rectal examination, absence

of withholding or fecal incontinence, extreme anal phobia)

### ***Investigations***

A thorough history and physical examination is usually sufficient to allow the practitioner to establish whether the child requires further investigation or has functional constipation. The presence of 'red flags' should alert the clinician to the possible need for further testing to exclude organic pathology. Metabolic tests, such as serum calcium level and thyroid function tests, X-ray abdomen, barium enema, anorectal manometry, suction rectal biopsy, colonic manometry, magnetic resonance imaging of the lumbosacral spine, and psychological evaluation may be helpful in order to rule out a possible organic cause of constipation. These should be performed in liaison with a paediatric gastroenterologist.

### ***Treatment***

The general approach to the child with functional constipation includes four sequential phases: parental education, elimination of the fecal mass if present, maintenance therapy to prevent fecal re-accumulation, and close follow-up for a sufficient time-period to adjust medications as necessary<sup>1,42</sup>. The education of the family should include the demystification of constipation and an explanation of its pathogenesis. Moreover, parents are encouraged to maintain a consistent, positive, and supportive attitude in all aspects of treatment. If a fecal mass is present, disimpaction must be carried out before initiation of maintenance therapy and may be accomplished by either the oral or rectal route. The oral approach is less invasive and gives a sense of power to the child, but adherence to the treatment regimen may be a problem, particularly given the increased fecal incontinence seen with the use of polyethylene glycol<sup>43</sup>. The rectal approach is faster but is invasive and may become more challenging with repeated use. Oral (with polyethylene glycol) and rectal disimpaction have been shown to be equally effective<sup>43</sup> and the choice of treatment is best determined after discussing the options with the family and child. Disimpaction with oral medication has been successfully reported with high doses of mineral oil, polyethylene glycol electrolyte solutions, or both<sup>44,45,46,47,48</sup>. Rectal disimpaction may be performed with phosphate, saline, or mineral oil enemas alone or in combination<sup>49,50</sup>. Once the impaction has been removed, the treatment focuses on maintenance therapy to prevent recurrence. This treatment consists of dietary interventions, behavioral modification, and laxatives to assure that bowel



movements occur at normal intervals with good evacuation. Multiple laxatives have been routinely used in the treatment of childhood constipation with a number of new agents currently being trialed, mostly in adults<sup>51</sup>. At the present time published evidence suggests that polyethylene glycol 3350 should be the laxative of first choice in pediatrics for functional constipation<sup>42,51,52,53,54</sup>. Enemas do not appear to carry any added benefit and should not be used routinely for maintenance therapy<sup>55</sup>. Increased intake of fluids and the use of absorbable and non-absorbable carbohydrate, and more recently pro- and pre-biotics, are commonly advised as methods to soften stools and improve defaecation frequency. Current evidence, however, does not support their routine use as supplementation over and above a normal intake, for the treatment of functional constipation<sup>51</sup>. Finally, an important component of treatment includes behavior modification and regular toilet habits, including unhurried time on the toilet after meals, although on their own these are unlikely to result in long-term sustained benefit<sup>56</sup>. Surgical interventions have little role in the management of functional constipation although there have been reports of success with the use of antegrade continence enemas in children with an intractable course<sup>57</sup>. Data on transcutaneous and sacral nerve stimulation is emerging and does not yet have a routine place in treatment<sup>58</sup>.

### ***Prognosis and long-term outcomes***

A systematic review of functional constipation follow-up studies suggested that almost two-thirds of children are found to be free from symptoms after 6 to 12 months of laxative treatment. Recovery rates appear to be better with early and sustained intervention with laxative treatment. Outcomes showed no relation with defecation frequency or positive family history and studies have been unable to identify a group of children at most risk of poor prognosis<sup>59,60,61</sup>. Long-term treatment and follow-up, with early therapeutic interventions of relapses remains an integral part of successful management of functional constipation<sup>42,62</sup>.

## **Chronic Intestinal Pseudo-obstruction**

### ***Introduction***

Chronic Intestinal Pseudo-Obstruction (CIPO) comprises a rare and heterogeneous group of conditions that variably affect one or more of the intrinsic gut components that govern intestinal motility namely the enteric nerves, muscles and interstitial cells of Cajal (ICCs) or affect their modulating influences. This impairs the ability of the intestine to propel its contents and CIPO is defined and characterised by repetitive episodes or continuous symptoms and signs of intestinal obstruction in the absence of a fixed, lumen-occluding lesion, which may be associated with radiological evidence of dilated bowel with fluid levels <sup>62,63</sup>. Although the true incidence and prevalence of CIPO conditions across the world are unclear, scanty epidemiological data suggest they are rare with an estimated incidence of approximately 1 in 40,000 live births <sup>64</sup>.

### ***Pathophysiology***

Conditions can be classified by whether they primarily affect intestinal smooth muscle (myopathies), nerves (neuropathies) or ICCs (mesenchymopathies) and can further be subdivided into primary or secondary, congenital or acquired, inheritance and what area of the gut they primarily involve <sup>63</sup>. CIPO in children most commonly occurs sporadically, is congenital and primary, and affects the intestine diffusely. At the present time, although mesenchymopathies have been implicated in a few reports, the majority of conditions are classified as neuropathies and myopathies <sup>65,66,67,68,69</sup>. For the majority this is adequately achieved through appropriate, often specialised, functional assessment and histopathology.

CIPO may also occur in association with other conditions affecting other systems of the body. Most commonly affected, more so in myopathies than neuropathies, is the urinary tract <sup>67</sup>. Specific conditions include hollow visceral myopathy and Megacystis—microcolon intestinal hypoperistalsis syndrome <sup>70</sup>. Other associations include connective tissue disorders, muscular dystrophies and autonomic disorders. CIPO may also occur secondary to intestinal surgery and a range of toxins, endocrine and metabolic defects. More recently, neuropathic viruses have been implicated in adult patients with CIPO <sup>71</sup>.

The genetics of CIPO is poorly characterised. In those that have been reported there appears to be a heterogeneous pattern of inheritance consisting of autosomal recessive (AR), autosomal dominant (AD) and X-linked (XL)<sup>72</sup>. Genes implicated include those for the transcription factor Sox10 (AD), filamin A (XL), and the L1 cell adhesion molecule (XL). CIPO is also seen in the context of mitochondrial disorders caused by mutations in the thymidine phosphorylase (Mitochondrial Neuro-Gastro-Intestinal Encephalomyopathy (MNGIE) syndrome) or in the polymerase-gamma genes (MNGIE without leukoencephalopathy)<sup>73</sup>.

### ***Clinical Presentation***

Patients with CIPO typically present with recurrent or continuous sub-occlusive episodes, which resemble intestinal mechanical obstruction. Patients with congenital CIPO typically present early in life with the majority being diagnosed within the first few weeks and months of life. Some of these will present in utero with a dilated urinary tract or abdominal distention. Approximately a third of children with congenital CIPO have intestinal malrotation<sup>67</sup>.

Symptoms vary according to age at presentation and the part of the gastrointestinal tract primarily affected. They commonly include vomiting (which is often bilious) and abdominal distension. Other symptoms variably include abdominal pain, anorexia, poor weight gain, constipation and diarrhoea. Other symptoms may result from involvement of other organ systems e.g. urinary tract (megacystis with increased bladder compliance and capacity and poor detrusor contractility, ureterohydronephrosis, recurrent UTIs). A most severe condition involving both the intestine and urinary system is megacystis-microcolon intestinal hypoperistalsis syndrome<sup>71</sup>. Symptoms may also be secondary to complications e.g. diarrhoea from bacterial overgrowth. Exacerbation of symptoms may be precipitated by various causes including intercurrent infections and stress.

The clinical course is generally characterised by relapses and remissions leading, in a small proportion, to gradual decompensation of intestinal function and ultimately to intestinal failure. This is more likely in severe cases, and those presenting late and/or that have been inadequately treated.

## ***Diagnosis***

Although this may be suspected from the clinical history (including family history) and course of the disease, it is often difficult because of the varied clinical presentation and limitations in the availability of specific or specialised diagnostic testing. Plain abdominal radiographs classically show a dilated gastrointestinal tract, which may contain air-fluid levels (Figure 1). Contrast studies often show marked delays in intestinal transit and may reveal other abnormalities such as malrotation and microcolon. Water-soluble contrast should be used instead of barium to prevent inspissation of contrast. Unfortunately, children with CIPO often undergo repeated and complex gastrointestinal surgery (including resection of dilated loops of bowel), which is neither diagnostic nor curative, before a diagnosis is finally made. A diagnosis of pseudo-obstruction should be suspected if there are symptoms of a generalised dysmotility (vomiting, abdominal distension and constipation) especially when they occur recurrently or chronically with no symptom free intervals. Associated urinary symptoms and autonomic nervous system dysfunction may also be suggestive. Review of previous radiological studies and histopathology may be helpful.

A more definitive diagnosis relies on following a number of specific steps:-

1. *Exclusion of any mechanical obstructive lesion* of the gastro-intestinal tract (X-rays, contrast studies or by previous exploratory surgery).
2. *Confirmation of abnormal motility* (functional motility testing e.g. oesophageal manometry, electrogastrography, gastric emptying studies, bowel transit studies, small and large bowel manometry). An abnormal small intestinal (antroduodenal) manometry study, with disruption of the phasic fasting motor activity, is classically associated with CIPO (Figure 2)<sup>73</sup>
3. *Search for an underlying cause* for the pseudo-obstruction, including potentially treatable ones. This may include, for example, assessment of haematological parameters, blood chemistry, metabolic screening, toxicology, infections, connective tissue diseases etc. Histopathological assessment is often valuable in the diagnosis and classification of CIPO. Limitations and variability in expertise and availability of specialised histopathological tools are a significant problem. International

initiatives are underway to improve the diagnostic yield and ultimate classification of CIPO disorders <sup>74,75,76</sup>.

Paediatric condition calcification has been recognised in children presenting with potential CIPO <sup>77</sup>. Small intestinal manometry in such children is often normal in direct contrast to those suffering from CIPO.

### ***Treatment***

Unfortunately the management of CIPO has seen little real progress and essentially remains supportive to:

1. maintain nutrition
2. preserve growth and development
3. limit symptoms and improve quality of life
4. limit complications such as bacterial overgrowth and life-threatening sepsis.

Nutrition aims to maintain maximally tolerated enteral feeds with use of parenteral nutrition (PN) as required. In our experience although most of the CIPO children had ileostomy formation to decompress the bowel and reduce afterload, three quarters of the myopathic CIPO remained dependent on PN as a main source of nutrition and fluid long-term as opposed to just over a third of the neuropathic CIPO patients. (N. Thapar, unpublished). Maintaining patients on maximally tolerated enteral nutrition preserves intestinal viability, enhances adaptation and limits associated complications e.g. hepatic cholestasis. Regimes to achieve this include specialised feeds and diets that transit the intestine most effectively and contain minimal residue. Continuous rather than bolus feeds via a gastrostomy or jejunostomy may be required <sup>78,79,80</sup>.

Drug use is largely limited to control of inflammation and immuno-modulation, and of bacterial overgrowth, with variable success reported with prokinetics <sup>80,81</sup>. The best studied and apparently most effective motility agents such as cisapride and tegaserod are no longer available given safety concerns. Newer agents are being developed but not routinely available at present. Many current regimes to enhance intestinal motility are anecdotal or based case reports and include the use of, for example, the somatostatin analogue octreotide in combination with erythromycin <sup>81</sup>. Sepsis by bacterial translocation or infection of

central venous lines is a major consideration and antibiotic use is a valuable part of treatment.

Surgery remains the most common intervention in patients with pseudo-obstruction with roles in diagnosis, feeding, symptom relief, bowel decompression, bypassing of diseased segments etc <sup>82</sup>. In our practise the majority of children with CIPO will have formation of an ostomy early in the course of the disease. Maintaining bowel decompression (nasogastric tubes, venting gastrostomies or jejunostomies, surgical stomas) is valuable not only for symptomatic relief but also helps limit further deterioration in effective motility secondary to chronic distension. It often reduces pseudo-obstructive episodes and enhances the tolerance of enteral feeding <sup>80,81,83</sup>. Electrical pacing of the gastrointestinal wall using implantable pacemakers provides a potential therapy but remains experimental at present.

Small bowel transplantation remains the only definitive cure with a number of centres reporting improved outcomes and survival <sup>83,83</sup>.

### ***Prognosis***

Intestinal pseudo-obstruction remains a serious life-threatening disease with devastating effects for patients and their families, including significantly impaired quality of life <sup>84</sup>. The mortality is not clear but is thought to be in the order of 20-30% long-term <sup>66,67</sup>. Increasing expertise in both the surgical and medical management has contributed to an improved prognosis especially to prevent complication such as sepsis and PN related liver disease. Outcomes from intestinal transplantation appear to be showing some improvement <sup>83,84</sup>.

### ***Summary and future perspectives***

CIPO presents a relatively rare but challenging group of conditions. Despite prolonged experience diagnosis remains difficult and management largely supportive. Initiatives to improve diagnosis and classification of disorders should help the identification and development of appropriate treatments. Recent advances raise possibilities for the use of novel pharmacologic agents and perhaps others such as cellular therapies to restore function.

## Gastrointestinal and nutritional problems in neurologically impaired children

### *Introduction*

The current increasing survival of children with severe central nervous system damage has created a major challenge for medical care. Although the primary problems for individuals with neuro-developmental disabilities are physical and mental incapacities, several clinical papers have reported that brain injuries may often result in significant gastrointestinal (GI) dysfunction<sup>85,86,87,88</sup>. The enteric nervous system includes more nerve cells than the spinal cord and thus it is not surprising that any insult to the central nervous system may affect the complex integrated capacities underlying feeding and nutrition<sup>89</sup>. Gastrointestinal and nutritional problems in neurologically impaired children have been recently recognized as an integral part of their disease, often leading to growth failure and worsened quality of life for both children and caregivers. The increased awareness of such conditions, together with a better understanding of their etiology and interplay, is essential to achieve an optimal global management of this group of children.

### *Feeding and nutritional aspects*

Historically, severe malnutrition has been accepted as an unavoidable and irremediable consequence of neurological impairment. Poor nutritional status was often marked by linear growth failure, decreased lean body mass, and diminished fat stores<sup>90,91</sup>. Over the past two to three decades, the development of multidisciplinary feeding programs providing comprehensive evaluation and management of feeding disorders in children with developmental disabilities have been proven to improve nutritional status and impact upon quality of life and a reduction in hospitalization rates<sup>92</sup>. Studies on small numbers of children with developmental disabilities have demonstrated that adequate nutritional support, provided by less invasive enteral access methods and better tolerated enteral formulae, may improve weight, muscle mass, subcutaneous energy stores, peripheral circulation, the healing of decubitus ulcers and general well-being, whilst at the same time decreasing irritability and spasticity<sup>93,94</sup>.

The true prevalence of undernutrition in neurologically impaired children is unknown. It has been estimated that approximately one-third are undernourished and many exhibit the consequences of malnutrition<sup>7</sup>. Yet, the prevalence and severity of malnutrition increases in parallel with the duration and

severity of neurological impairment<sup>95,96,97</sup>. The predominant nutritional deficit is in energy intake, given that only 20% of these children are regularly ingesting 100% of their estimated average requirement. Moreover, half of the children with severe disabilities consumed less than 81% of the reference nutrient intake for copper, iron, magnesium, and zinc, influenced largely by their large consumption of milk<sup>98</sup>.

Nutritional support is essential for the care of neurologically impaired children. An individualized management plan accounting for the child's nutritional status, feeding ability, and medical condition should be determined. Energy requirements must be individualized considering muscle tone, mobility, activity level, altered metabolism and growth. In order to increase energy intake, the easiest and least invasive approach is to improve oral intake. Food caloric density may be increased by adding modular nutrients, modifying recipes or using high-calorie formulae. Children who cannot chew effectively may be able to receive the same foods blended into a puree of acceptable consistency. Those who can tolerate solids but not liquids can have commercial thickeners added to their fluids. Oral feeding skills may be improved with rehabilitation therapy, even if the results are often disappointing<sup>99,100,101</sup>. Adequate positioning of the child during meals and appropriate food temperature are also important. However, oral intake can be maintained as long as the child is growing well, there is no risk of aspiration, and the feeding time remains within acceptable limits. When oral intake is insufficient, unsafe, or too time-consuming enteral nutrition should be initiated.

The type of enteral access will depend on the anticipated duration of enteral nutrition support as well as the clinical status of the child. Nasogastric tubes are minimally invasive but are easily dislodged and may be associated with local complications such as otitis, sinusitis, congestion, and skin irritation. Therefore, nasogastric feeds should only be used for short-term nutritional support (usually less than three months). When long-term enteral nutrition support is required, a gastrostomy should be considered. Although more invasive, gastrostomies are more convenient and esthetically acceptable. Gastrostomy placement has been shown to reduce feeding time, food-related choking episodes, frequency of chest infections, family stress, and to improve weight and nutritional status significantly in children with severe neurologic impairment<sup>95,102</sup>. Percutaneous gastrostomy (PEG), however, is not without complications or concerns. Minor catheter infections, perforation and an overall reduced length of survival have been described in both adult and pediatric populations<sup>103,103,104,105,106,107</sup>.



The anatomy and function of the stomach should be carefully evaluated before the placement of the feeding tube. The coexistence of gastro-oesophageal reflux may require a simultaneous fundoplication, and delayed gastric emptying may necessitate consideration of pyloroplasty or duodenal placement of the distal portion of the tube. Physiologically designed formulas of increased caloric and protein density can be used for gastric and nasogastric infusion, as palatability is no longer an issue. The choice between bolus and drip may depend on oesophago-gastric function, the volume to be delivered, or the home care needs of the child and his or her caregivers. Often patients may benefit from a combination of daytime bolus and nocturnal continuous feeds, with the latter providing 30-50% of the child's nutrient needs thus allowing more freedom for daily activities. When safety of oral feeding is not an issue, these enteral techniques can merely supplement the child's own nutrition, with caregivers continuing to feed the child actively. This dual feeding method often provides great satisfaction to parents and caregivers given the mealtime interaction is improved when there is no longer need for force-feeding of medication or nourishment.

### *Gastrointestinal problems*

Chronic gastrointestinal disorders are very common in neurologically impaired children, with a reported prevalence of up to 92%<sup>108</sup>. Dysphagia, rumination, gastro-oesophageal reflux (GOR), delayed gastric emptying, abdominal pain and constipation have all been described in this group of children, potentially contributing to feeding difficulties and carrying challenging long-term management issues.

### *Dysphagia*

Oro-motor dysfunction is a frequent concomitant issue and often one of the first signs of neuromuscular impairment. Related swallowing problems have been shown to affect up to 90% of neurologically impaired children, and is a major contributor to malnutrition<sup>86</sup>. This is not surprising since the development of oral-motor skills mirrors general neurological maturation and requires coordination of the movement of several striated muscles in the mouth, pharynx and oesophagus, which are under the control of six cranial nerves, the brain stem and the cerebral cortex. In addition, anatomic abnormalities such as cleft palate, laryngeal clefts, and tracheoesophageal fistula may accompany neurologic deficits as part of congenital or genetic syndromes. Dysphagia may manifest as distress during meals (including coughing, choking, and refusal of feeding),

chronic or episodic aspiration-related respiratory disorders, and failure to thrive. Barium swallow, cine-swallow, radionuclide esophageal clearance scan, and oesophageal manometry may all be of some help in the clinical assessment. Successful management of dysphagia is central to the child's well-being and ability to achieve his or her potential. Neurologically impaired children often show greater problems with liquid foods, thus requiring the use of thickener products. Oral motor exercise approaches using sensory modalities may help improving muscle strength and oral coordination. Nevertheless, in most cases, the presence of unsafe swallows and/or prolonged distressing mealtimes finally leads to the use of enteral rather than oral nutrition.

#### *Gastro-oesophageal reflux.*

Several reports have demonstrated a high incidence of GOR in children with neurological impairment. Increased intra-abdominal pressure secondary to spasticity and scoliosis, prolonged supine position, and co-existing hiatal hernia have been attributed as contributing factors to the increased frequency of GOR. Central nervous system dysfunction, however, is likely to be the primary cause, with GOR being part of the generalized dysmotility of the foregut or indeed the entire intestine. Decreased resting pressure and increased frequency of transient relaxations of the lower oesophageal sphincter, together with oesophageal motility abnormalities, are probably a consequence of neuromuscular incoordination.

Currently the most accurate way of diagnosing GOR is 24-hour oesophageal pH impedance recording, which allows not only the quantification of reflux episodes but also helps in establishing the temporal relationship between GOR and the symptom complex in question. The diagnostic work-up should then include upper GI endoscopy with multiple oesophageal biopsies and upper GI barium study, in order to evaluate the mucosa and to look for the possible presence of strictures, diverticuli, or hiatal herniae. Radionuclide studies such as gastric scintigraphy should also be performed, given the higher incidence of delayed gastric emptying which may contribute to GOR<sup>109,110</sup>. An oesophageal manometry evaluating visceral motility may be helpful to detect the underlying pathophysiological mechanisms, especially when surgery is being considered.

Although children with neurologic impairment are more likely to have intractable reflux and eventually require some surgical procedures, medical therapy should be tried first. When surgery is required, the Nissen

fundoplication is currently the most widely used technique to strengthen the anti-reflux barrier and relieve symptoms.

### *Constipation*

Infrequent stool passage and hard bowel movements are very common in neurologically impaired children. Total and sequential colonic transit times have been reported being prolonged and delayed mainly at the level of the left colon and rectum in this group of children, implying a probable defect in gut innervation<sup>88</sup>. The problem is usually exacerbated by prolonged immobility, inadequate fiber intake, and concurrent medications. Unfortunately, recognition and effective management of constipation are often postponed because other disabilities overshadow those related to defecation. The therapeutic approach needs to be tailored to the individual patient. Oral or rectal disimpaction should be followed by promotion of regular bowel habit, through dietary modification, positioning, and use of laxative medications. A significant number of children with neurological impairment needs to be on chronic doses of laxatives. This medical management is usually effective in enabling regular defecation, but where it fails, consideration should be given to a surgically placed appendicostomy.

## Cyclical Vomiting Syndrome

### *Introduction*

Cyclic vomiting syndrome (CVS) is a disorder characterized by recurrent, stereotypical episodes of intense nausea and vomiting lasting few hours to days interspersed with symptom-free periods of varying length <sup>111</sup>. In the majority of cases the underlying mechanisms remain unknown and patients are labeled as having idiopathic CVS. In children, the incidence of new cases has been reported to be 3.15/100,000 children per year, suggesting that CVS is more common than previously thought <sup>112</sup>. Although CVS may occur in all age groups the average age at initial diagnosis is 5 years with often a delay in diagnosis of several years. In children with CVS, there is a recognized association with a personal history of headache or migraine (in up to 45%) and family history of migraine. CVS has a substantially negative impact on children's quality of life, given that hospital admissions during the acute phase are rather common and that the condition significantly affects children's activities of daily living and academic time <sup>113</sup>.

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### *Pathophysiology*

The pathogenesis of CVS remains poorly understood and different mechanisms have been suggested including mitochondrial DNA (mtDNA) mutations responsible for deficits in cellular energy production, heightened hypothalamic-pituitary-adrenal (HPA) axis activation and autonomic nervous system (ANS) dysfunction <sup>114,115,116</sup>. A unifying theory has recently been hypothesized suggesting that psychological and physical stress conditions initiate the cascade of HPA axis activation by releasing corticotrophin-releasing factor (CRF), which in turn inhibits the foregut motility by activating the inhibitory motor neurons in the dorsal motor nucleus of the vagus, and increases the adrenergic tone by activating the locus ceruleus in the lateral floor of the fourth ventricle. In concert, during stress conditions when needs are increased the impaired cellular energy production due to mtDNA mutations is unable to meet the heightened demand and predisposes individuals to the onset of vomiting cycle, and perpetuates the dysfunction of the autonomic neurons because of their high energy requirement.

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### ***Clinical presentation***

CVS has a typical on-off temporal pattern and is usually characterized by 4 different phases: 1. *The interepisodic or well phase*, which occurs between the vomiting episodes when the child is relatively symptom-free, and lasts weeks to months. 2. *The prodromal phase*, which is usually characterised by intense nausea, anorexia, pallor, lethargy and headache, and lasts minutes to hours. Usually, during this phase the child is still able to take and retain oral medication. 3. *The emetic phase*, during which the most common symptoms are intense nausea, vomiting, retching, listlessness, pallor, hypothermia or low grade fever, prostration, abdominal pain, diarrhoea, photophobia, phonophobia and hypertension in the Sato variant. The episodes may last from hours to days (up to 10 days), with a median duration of 24-27 hours. The frequency of the emetic phases ranges from 1 to 70 per year with an average of 12 episodes a year, and the number of emeses during each attack is at least 4 times/hour for at least 1 hour. It usually occurs early morning (2-4 a.m.) or upon awakening (6-8 a.m.), and each episode tends to be stereotypical for each patient regarding the time of onset, the duration, intensity and symptomatology. Many patients show unusual specific behaviour features during the attacks aimed at lessening the intense nausea, such as being irritable, verbally abusive, and demanding, taking long hot showers or baths, drinking compulsively, and remaining in the foetal position in a dark and quiet room. Finally, various complications may occur as consequence of intense and repetitive episodes of vomiting including dehydration and electrolytes imbalance, peptic esophagitis, gastritis and hematemesis due to Mallory-Weiss tears, weight loss and dental caries. Specific triggering factors are identified in almost two third of patients including psychological stressors (holiday, birthday, vacation, parental or interpersonal conflict), physical stressors (lack of sleep, excess physical exhaustion, menses), infections (upper respiratory infections, sinusitis) and dietary factors (glutamate, chocolate, cheese, allergy). 4. *The recovery phase*, which begin when vomiting and nausea terminate and end when the child return to the normal activity.

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### ***Diagnosis***

The diagnosis of CVS is primarily based on history and clinical presentation fulfilling the diagnostic criteria developed by North American Society for Pediatric Gastroenterology, Hepatology and Nutrition, in the absence of other possible causes with similar presentation (Table 1) <sup>117</sup>. There are no specific tests to

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diagnose CVS, and currently the basic assessment includes FBC, amylase, lipase, liver function test, basic metabolic profile (glucose, BUN and electrolytes), and upper gastrointestinal contrast study to rule out anatomical abnormalities. In the presence of warning signals, such as bilious vomiting, severe abdominal pain, abdominal tenderness, episodes triggered by either fasting or high-protein meals, and abnormal neurological findings, further specific investigations should be promptly considered and tailored to the individual patient presentation. For instance, if there is a suspicion of metabolic and endocrine disorders additional laboratory tests, such as lactate, pyruvate, organic acid and amino acid analysis, plasma carnitine and acylcarnitine, plasma cortisol levels, and urinary porphyrins should be performed. Abdominal ultrasound, abdominal CT scan and upper gastrointestinal endoscopy should be considered in the presence of gastrointestinal alarm symptoms and signs. Finally, brain magnetic resonance imaging should be performed if a patient has neurologic manifestations. The differential diagnosis of disorders mimicking CVS is extensive and partially summarised in Table 2.

### **Management**

The treatment of CVS is aimed at avoiding the trigger factors, terminating the acute phase, and preventing or reducing the frequency and intensity of acute episodes. Supportive and abortive measures during the acute episode include a dark and quiet environment, intravenous fluid, rescue agents as Ondansetron, Lorazepam and Chlorpromazine, and in older children Sumatriptan as an abortive agent <sup>118</sup>. Prophylactic therapies are usually provided for those children with high recurrence and severity of episodes, and include as first-line agents Cyproheptadine, Pizotifen, and Amitriptyline, and Propanolol as a second line approach (8). In the last few years, the use of mitochondrial supplements, such as Riboflavin, L-carnitin and CoQ10, have been gradually increased based upon evidence of their efficacy in migraine.

### **Prognosis**

Although the above treatments are effective in more than two third of cases, the management remains unsatisfactory in a significant number of the children who are referred to tertiary and quaternary centers.

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**Table 1**

**Diagnostic criteria for children with cyclical vomiting syndrome suggested by the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition Consensus Statement (7)**

1. At least 5 attacks in any interval, or a minimum of 3 attacks during a 6 month period
2. Episodic attacks of intense nausea and vomiting lasting 1 hr-10 days and occurring at least 1 wk apart
3. Stereotypical pattern and symptoms in the individual patient
4. Vomiting during attacks occurs at least 4 times/hr for at least 1 hr
5. Return to baseline health between episodes
6. Not attributable to another disorder

**All of the criteria must be met to meet this consensus definition of CVS.**

**Table 2**

**Differential diagnosis of cyclical vomiting in children and adolescents**

***Gastrointestinal disorders***

- Bowel obstruction (malrotation with volvulus, duplication cyst, and intermittent intestinal intussusception)
- Inflammatory diseases (gastritis, duodenitis, peptic ulcer disease, IBD=)
- Pancreatic diseases (pancreatitis and pancreatic pseudocyst)
- Hepatobiliary disease (hepatitis)

***Infections***

- Enteritis
- Otitis media, chronic sinusitis, and hepatitis

***Neurologic disorders***

- Migraine
- Epilepsy
- Space occupying central nervous system lesions (hydrocephalus, posterior fossa tumors, subdural hematoma, and subdural effusion)
- Familial dysautonomia

***Metabolic and endocrine disorders***

- Diabetes mellitus, Addison disease, and pheochromocytoma



- Aminoaciduria, organic aciduria, fatty acid oxidation disorders, mitochondrial disorders, and urea cycle defects

***Medications and toxins***

- Antibiotics, NSAID, laxatives, hormones, etc.

***Urologic/gynaecological disorders***

- Pelvi-ureteric junction obstruction
- Nephrolithiasis

***Miscellaneous disorders***

- Abdominal migraines
  - Asthma
  - Benign paroxysmal positional vertigo
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## REFERENCES

- <sup>1</sup> Chiou E, Nurko S. Functional abdominal pain and irritable bowel syndrome in children and adolescents. *Therapy* 2011;8:315-331.
- <sup>2</sup> Hyman PE, Milla PJ, Benninga MA, Davidson GP, Fleisher DF, Taminiu J. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* 2006;130:1519-1526.
- <sup>3</sup> Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. *Gastroenterology* 2006;130:1527-1537.
- <sup>4</sup> Starfield B, Hoekelman RA, McCormick M, Benson P, Mendenhall RC, Moynihan C, et al. Who provides health care to children and adolescents in the United States? *Pediatrics* 1984;74:991-997.
- <sup>5</sup> Crushell E, Rowland M, Doherty M, Gormally S, Harty S, Bourke B, et al. Importance of parental conceptual model of illness in severe recurrent abdominal pain. *Pediatrics* 2003;112:1368-1372.
- <sup>6</sup> Chiou E, Nurko S. Management of functional abdominal pain and irritable bowel syndrome in children and adolescents. *Expert Rev Gastroenterol Hepatol* 2010;4:293-304.
- <sup>7</sup> Tam YH, Chan KW, To KF, Cheung ST, Mou JW, Pang KK, et al. Impact of pediatric Rome III criteria of functional dyspepsia on the diagnostic yield of upper endoscopy and predictors for a positive endoscopic finding. *J Pediatr Gastroenterol Nutr* 2011;52:387-391.
- <sup>8</sup> Chitkara DK, Rawat DJ, Talley NJ. The epidemiology of childhood recurrent abdominal pain in Western countries: a systematic review. *Am J Gastroenterol* 2005;100:1868-1875.
- <sup>9</sup> Hyams JS, Hyman PE. Recurrent abdominal pain and the biopsychosocial model of medical practice. *J Pediatr* 1998;133:473-478.
- <sup>10</sup> Buonavolonta R, Coccorullo P, Turco R, Boccia G, Greco L, Staiano A. Familial aggregation in children affected by functional gastrointestinal disorders. *J Pediatr Gastroenterol Nutr* 2010;50:500-505.
- <sup>11</sup> Drossman DA, Li Z, Leserman J, Toomey TC, Hu YJ. Health status by gastrointestinal diagnosis and abuse history. *Gastroenterology* 1996;110:999-1007.
- <sup>12</sup> Saps M, Lu P, Bonilla S. Cow's-milk allergy is a risk factor for the development of FGIDs in children. *J Pediatr Gastroenterol Nutr* 2011;52:166-169.
- <sup>13</sup> Campo JV, Bridge J, Lucas A, Savorelli S, Walker L, Di Lorenzo C, et al. Physical and emotional health of mothers of youth with functional abdominal pain. *Arch Pediatr Adolesc Med* 2007;161:131-137.
- <sup>14</sup> Yacob D, Di Lorenzo C, Bridge JA, Rosenstein PF, Onorato M, Bravender T, et al. Prevalence of pain-predominant functional gastrointestinal disorders and somatic symptoms in patients with anxiety or depressive disorders. *J Pediatr* 2013;163:767-770.
- <sup>15</sup> Bonilla S, Saps M. Early life events predispose the onset of childhood functional gastrointestinal disorders. *Rev Gastroenterol Mex* 2013;78:82-91.
- <sup>16</sup> Saps M, Bonilla S. Early life events: infants with pyloric stenosis have a higher risk of developing chronic abdominal pain in childhood. *J Pediatr* 2011;159:551-554 e551.
- <sup>17</sup> Tanaka Y, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial model of irritable bowel syndrome. *J Neurogastroenterol Motil* 2011;17:131-139.

- 
- <sup>18</sup> Di Lorenzo C, Colletti RB, Lehmann HP, Boyle JT, Gerson WT, Hyams JS, et al. Chronic Abdominal Pain In Children: a Technical Report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2005;40:249-261.
- <sup>19</sup> Dodge JA. Recurrent abdominal pain in children. *Br Med J* 1976;1:385-387.
- <sup>20</sup> Gomara RE, Halata MS, Newman LJ, Bostwick HE, Berezin SH, Cukaj L, et al. Fructose intolerance in children presenting with abdominal pain. *J Pediatr Gastroenterol Nutr* 2008;47:303-308.
- <sup>21</sup> Guandalini S, Magazzu G, Chiaro A, La Balestra V, Di Nardo G, Gopalan S, et al. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. *J Pediatr Gastroenterol Nutr* 2010;51:24-30.
- <sup>22</sup> Huertas-Ceballos A, Logan S, Bennett C, Macarthur C. Psychosocial interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. *Cochrane Database Syst Rev* 2008:CD003014.
- <sup>23</sup> Rutten JM, Reitsma JB, Vlieger AM, Benninga MA. Gut-directed hypnotherapy for functional abdominal pain or irritable bowel syndrome in children: a systematic review. *Arch Dis Child* 2013;98:252-257.
- <sup>24</sup> Vlieger AM, Rutten JM, Govers AM, Frankenhuis C, Benninga MA. Long-term follow-up of gut-directed hypnotherapy vs. standard care in children with functional abdominal pain or irritable bowel syndrome. *Am J Gastroenterol* 2012;107:627-631.
- <sup>25</sup> Saps M, Youssef N, Miranda A, Nurko S, Hyman P, Cocjin J, et al. Multicenter, randomized, placebo-controlled trial of amitriptyline in children with functional gastrointestinal disorders. *Gastroenterology* 2009;137:1261-1269.
- <sup>26</sup> Campo JV, Perel J, Lucas A, Bridge J, Ehmann M, Kalas C, et al. Citalopram treatment of pediatric recurrent abdominal pain and comorbid internalizing disorders: an exploratory study. *J Am Acad Child Adolesc Psychiatry* 2004;43:1234-1242.
- <sup>27</sup> Ford AC, Talley NJ, Spiegel BM, Foxx-Orenstein AE, Schiller L, Quigley EM, et al. Effect of fibre, antispasmodics, and peppermint oil in the treatment of irritable bowel syndrome: systematic review and meta-analysis. *BMJ* 2008;337:a2313.
- <sup>28</sup> Sadeghian M, Farahmand F, Fallahi GH, Abbasi A. Cyproheptadine for the treatment of functional abdominal pain in childhood: a double-blinded randomized placebo-controlled trial. *Minerva Pediatr* 2008;60:1367-1374.
- <sup>29</sup> Tack J. Prokinetics and fundic relaxants in upper functional GI disorders. *Curr Opin Pharmacol* 2008;8:690-696.
- <sup>30</sup> Huertas-Ceballos A, Logan S, Bennett C, Macarthur C. Pharmacological interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood. *Cochrane Database Syst Rev* 2008:CD003017.
- <sup>31</sup> Lembo AJ, Conboy L, Kelley JM, Schnyer RS, McManus CA, Quilty MT, et al. A treatment trial of acupuncture in IBS patients. *Am J Gastroenterol* 2009;104:1489-1497.
- <sup>32</sup> Benninga MA, Mayer EA. The power of placebo in pediatric functional gastrointestinal disease. *Gastroenterology*. 2009 Oct;137(4):1207-1210.
- <sup>33</sup> Apley J, Hale B. Children with recurrent abdominal pain: how do they grow up? *Br Med J* 1973;3:7-9.
- <sup>34</sup> Christensen MF, Mortensen O. Long-term prognosis in children with recurrent abdominal pain. *Arch Dis Child* 1975;50:110-114.

- 
- <sup>35</sup> Magni G, Pierri M, Donzelli F. Recurrent abdominal pain in children: a long term follow-up. *Eur J Pediatr* 1987;146:72-74.
- <sup>36</sup> Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. *Best Pract Res Clin Gastroenterol*. 2011 Feb;25(1):3-18.
- <sup>37</sup> Baker S, Liptak G, Colletti R, et al. Evaluation and treatment of constipation in infants and children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Constipation Guideline Committee of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2006Sep;43(3):e1-13.
- <sup>38</sup> Molnar D, Taitz LS, Urwin OM, Wales JK. Anorectal manometry results in defecation disorders. *Arch Dis Child* 1983;58:257-261.
- <sup>39</sup> Partin JC, Hamill SK, Fischel JE, Partin JS. Painful defecation and fecal soiling in children. *Pediatr* 1992;89:1007-1009.
- <sup>40</sup> Borowitz SM, Cox DJ, Tam A, et al. Precipitants of constipation during early childhood. *J Amer Board Fam Pract* 2003;16:213-218.
- <sup>41</sup> Hyman PE, Fleisher D. Functional fecal retention. *Pract Gastroenterol* 1992;31:29-37.
- <sup>42</sup> Mugie SM, Di Lorenzo C, Benninga MA. Constipation in childhood. *Nat Rev Gastroenterol Hepatol*. 2011 Aug 2;8(9):502-511.
- <sup>43</sup> Bekkali NL, van den Berg MM, Dijkgraaf MG, van Wijk MP, Bongers ME, Liem O, Benninga MA. Rectal fecal impaction treatment in childhood constipation: enemas versus high doses oral PEG. *Pediatrics*. 2009 Dec;124(6):e1108-1115.
- <sup>44</sup> Tolia V, Lin CH, Elitsur Y. A prospective randomized study with mineral oil and oral lavage solution for treatment of faecal impaction in children. *Aliment Pharmacol Ther* 1993;7:523Y9.
- <sup>45</sup> Gleghorn EE, Heyman MB, Rudolph CD. No-enema therapy for idiopathic constipation and encopresis. *Clin Pediatr* 1991;30:667-672.
- <sup>46</sup> Ingebo KB, Heyman MB. Polyethylene glycol-electrolyte solution for intestinal clearance in children with refractory encopresis: a safe and effective therapeutic program. *Am J Dis Child* 1988;142:340-342.
- <sup>47</sup> Youssef NN, Peters JM, Henderson W, et al. Dose response of PEG 3350 for the treatment of childhood fecal impaction. *J Pediatr* 2002;141:410-414.
- <sup>48</sup> Ferguson A, Culbert P, Gillett H, Barras N. New polyethylene glycol electrolyte solution for the treatment of constipation and faecal impaction. *Ital J Gastroenterol Hepatol* 1999;31(Suppl 3):S249Y52.
- <sup>49</sup> Nurko SS, Garcia Y, Aranda JA, et al. Treatment of intractable constipation in children: experience with Cisapride. *J Pediatr Gastroenterol Nutr* 1996;22:38-44.
- <sup>50</sup> Cox DJ, Sutphen J, Borowitz S, et al.. Simple electromyographic biofeedback treatment for chronic pediatric constipation/encopresis: Preliminary report. *Biofeedback Self Regul* 1994;19:41-50.
- <sup>51</sup> Hoekman DR, Benninga MA. Functional constipation in childhood: current pharmacotherapy and future perspectives. *Expert Opin Pharmacother*. 2013 Jan;14(1):41-51.
- <sup>52</sup> Baker S, Liptak G, Colletti R, et al. Evaluation and treatment of constipation in children: summary of updated recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *J Pediatr Gastroenterol Nutr* 2000Jan;30(1):109.

- 
- <sup>53</sup> Staiano A. Use of polyethylene glycol solution in functional and organic constipation in children. *Ital J Gastroenterol Hepatol* 1999;31(Suppl 3):S260-263.
- <sup>54</sup> Pashankar DS, Bishop WP, Loening-Baucke V. Long-term efficacy of polyethylene glycol 3350 for the treatment of chronic constipation in children with and without encopresis. *Clin Pediatr* 2003;42:815-819.
- <sup>55</sup> Bongers ME, van den Berg MM, Reitsma JB, Voskuil WP, Benninga MA. A randomized controlled trial of enemas in combination with oral laxative therapy for children with chronic constipation. *Clin Gastroenterol Hepatol*. 2009 Oct;7(10):1069-1074.
- <sup>56</sup> Lowery SP, Srour JW, Whitehead WE, Schuster NM. Habit training as treatment of encopresis secondary to chronic constipation. *J Pediatr Gastroenterol Nutr* 1985;4:397-401.
- <sup>57</sup> Mugie SM, Machado RS, Mousa HM, et al. Ten-Year Experience Using Antegrade Enemas in Children. *J Pediatr*. 2012;161:700-704.
- <sup>58</sup> Van Wunnik BP, Baeten CG, Southwell BR. Neuromodulation for constipation: sacral and transcutaneous stimulation. *Best Pract Res Clin Gastroenterol*. 2011;25:181-191.
- <sup>59</sup> Pijpers MA, Bongers ME, Benninga MA, Berger MY. Functional constipation in children: a systematic review on prognosis and predictive factors. *J Pediatr Gastroenterol Nutr*. 2010 Mar;50(3):256-268.
- <sup>60</sup> Bongers MEJ, van Wijk MP, et al Long-term prognosis for childhood constipation: clinical outcomes in adulthood. *Pediatrics*. 2010;126:e156-162.
- <sup>61</sup> van den Berg MM, van Rossum CH, de Lorijn F, et al. Functional constipation in infants: a follow-up study. *J Pediatr*. 2005;147:700-4.
- <sup>62</sup> Rudolph CD, Hyman PE, Altschuler SM, Christensen J, Colletti RB, Cucchiara S, Di Lorenzo C, Flores AF, Hillemeier AC, McCallum RW, Vanderhoof JA. Diagnosis and treatment of chronic intestinal pseudo-obstruction in children: report of consensus workshop. *J Pediatr Gastroenterol Nutr* 1997;24:102-112
- <sup>63</sup> Hyman P and Thapar N. *Pediatric Neurogastroenterology: Gastrointestinal Motility and Functional Disorders in Children, Clinical Gastroenterology*. Eds. Faure, Di Lorenzo and Thapar. Springer Inc. 2013;257-270
- <sup>64</sup> Vargas JH, Sachs P, Ament ME. Chronic intestinal pseudo-obstruction syndrome in pediatrics. Results of a national survey by members of the North American Society of Pediatric Gastroenterology and Nutrition. *J Pediatr Gastroenterol Nutr* 1989;7:323- 332
- <sup>65</sup> Mousa H, Hyman PE, Cocjin J, Flores AF, Di Lorenzo C. Long-term outcome of congenital intestinal pseudoobstruction. *Dig Dis Sci*. 2002 Oct;47(10):298-305
- <sup>66</sup> Heneyke S, Smith VV, Spitz L, Milla PJ. Chronic intestinal pseudo-obstruction: treatment and long term follow up of 44 patients. *Arch Dis Child*. 1999 Jul;81(1):21-27.
- <sup>67</sup> Streutker CJ, Huizinga JD, Campbell F, Ho J, Riddell RH. Loss of CD117 (c-kit)- and CD34-positive ICC and associated CD34-positive fibroblasts defines a subpopulation of chronic intestinal pseudo-obstruction. *Am J Surg Pathol* 2003;27:228-235.
- <sup>68</sup> Jain D, Moussa K, Tandon M, Culpepper-Morgan J, Proctor DD. Role of interstitial cells of Cajal in motility disorders of the bowel. *Am J Gastroenterol* 2003;98:618-624.
- <sup>69</sup> Struijs MC, Diamond IR, Pencharz PB, Chang KT, Viero S, Langer JC, Wales PW. Absence of the interstitial cells of Cajal in a child with chronic pseudoobstruction. *J Pediatr Surg*. 2008 Dec;43(12):e25-29

- 
- <sup>70</sup> Gosemann JH, Puri P. Megacystis microcolon intestinal hypoperistalsis syndrome: systematic review of outcome. *Pediatr Surg Int*. 2011 Oct;27(10):1041-1046.
- <sup>71</sup> De Giorgio R, Ricciardiello L, Naponelli V, Selgrad M, Piazzini G, Felicani C, Serra M, Fronzoni L, Antonucci A, Cogliandro RF, Barbara G, Corinaldesi R, Tonini M, Knowles CH, Stanghellini V. Chronic intestinal pseudo-obstruction related to viral infections. *Transplant Proc*. 2010 Jan-Feb;42(1):9-14.
- <sup>72</sup> Panza E, Knowles CH, Graziano C, Thapar N, Burns AJ, Seri M, Stanghellini V, De Giorgio R. Genetics of human enteric neuropathies. *Prog Neurobiol*. 2012 Feb;96(2):176-189.
- <sup>73</sup> Borrelli O, Giorgio V and Thapar N. Antroduodenal Manometry. *Pediatric Neurogastroenterology: Gastrointestinal Motility and Functional Disorders in Children, Clinical Gastroenterology*. Eds. Faure, Di Lorenzo and Thapar. Springer Inc. 2013;91-105.
- <sup>74</sup> Knowles et al *Acta Neuropathol* (2009) 118:271–301.; Knowles et al *Acta Neuropathol* (2009) 118:271–301.
- <sup>75</sup> Knowles et al *Gut* 2010;59:882-887.
- <sup>76</sup> Knowles et al *Neurogastroenterol Motil* (2011) 23, 115–124.
- <sup>77</sup> Hyman PE, Bursch B, Beck D, DiLorenzo C, Zeltzer LK. Discriminating pediatric condition falsification from chronic intestinal pseudo-obstruction in toddlers. *Child Maltreat*. 2002 May;7(2):132-137.
- <sup>78</sup> Di Lorenzo C, Flores AF, Buie T, Hyman PE. Intestinal motility and jejunal feeding in children with chronic intestinal pseudo-obstruction. *Gastroenterology*.1995 May;108(5):1379-1385.
- <sup>79</sup> Garipey CE, Mousa H. Clinical management of motility disorders in children. *Semin Pediatr Surg*. 2009 Nov;18(4):224-238
- <sup>80</sup> Di Lorenzo C, Youssef NN. Diagnosis and management of intestinal motility disorders. *Semin Pediatr Surg*. 2010 Feb;19(1):50-58.
- <sup>81</sup> Di Lorenzo C, Lucanto C, Flores AF, Idries S, Hyman PE. Effect of sequential erythromycin and octreotide on antroduodenal manometry. *J Pediatr Gastroenterol Nutr*. 1999 Sep;29(3):293-296.
- <sup>82</sup> Mugie SM, Di Lorenzo C. From ACE to replace: role of surgery and transplantation in motility disorders. *J Pediatr Gastroenterol Nutr*. 2011 Dec;53 Suppl 2:S59-61.
- <sup>83</sup> Millar AJ, Gupte G, Sharif K. Intestinal transplantation for motility disorders. *Semin Pediatr Surg*. 2009 Nov;18(4):258-262
- <sup>84</sup> Schwankovsky L, Mousa H, Rowhani A, Di Lorenzo C, Hyman PE. Quality of life outcomes in congenital chronic intestinal pseudo-obstruction. *Dig Dis Sci*. 2002 Sep;47(9):1965-1968.
- <sup>85</sup> Reilly S, Skuse D, Poblete X. Prevalence of feeding problems and oral motor dysfunction in children with cerebral palsy: a community survey. *J Pediatr* 1996;129:877-882.
- <sup>86</sup> Sondheimer JM, Morris BA. Gastroesophageal reflux among severely retarded children. *J Pediatr* 1979;94:710-714.
- <sup>87</sup> Staiano A, Del Giudice E. Colonic transit and anorectal manometry in children with severe brain damage. *Pediatrics* 1994;94:169-173.
- <sup>88</sup> Ravelli AM, Milla PJ. Vomiting and gastroesophageal motor activity in children with disorders of the central nervous system. *J Pediatr Gastroenterol Nut* 1998;26:56-63.

- 
- <sup>89</sup> Menkes JH and Ament ME. Neurologic disorders of gastroesophageal function. *Advances in Neurology* 188;49: 409-416.
- <sup>90</sup> Patrick J, Boland M, Stoski D, Murray GE. Rapid correction of wasting in children with cerebral palsy. *Dev Med Child Neurol* 1986;28:734-739
- <sup>91</sup> Stallings VA, Cronk CE, Zemel BS, Charney EB. Body composition in children with spastic quadriplegic cerebral palsy. *J Pediatr* 1995;126:833-839
- <sup>92</sup> Schwartz SM, Corredor J, Fisher-Medina J, et al. Diagnosis and treatment of feeding disorders in children with developmental disabilities. *Pediatrics* 2001;108:671-676
- <sup>93</sup> Rempel GR, Colwell S, Nelson RP. Growth in children with cerebral palsy fed via gastrostomy. *Pediatrics* 1988;857-862
- <sup>94</sup> Sanders KD, Cox K, Cannon R, et al. Growth response to enteral feeding by children with cerebral palsy. *J Parenter Enteral Nutr* 1990;14:23-26
- <sup>95</sup> Stallings VA, Charney EB, Davies JC, Cronk CE. Nutritional status and growth of children with diplegic or hemiplegic cerebral palsy. *Dev Med Child Neurol* 1993;35:997-1006.
- <sup>96</sup> Stevenson RD, Hayes RP, Cater LV, Blackman JA. Clinical correlates of linear growth in children with cerebral palsy. *Dev Med Child Neurol* 1994;36:135-142.
- <sup>97</sup> Sánchez-Lastres J, Eirís-Puñal J, Otero-Cepeda JL, Pavón-Belinchón P, Castro-Gago M. Nutritional status of mentally retarded children in north-west Spain. I. Anthropometric indicators. *Acta Paediatr* 2003;92:747-753.
- <sup>98</sup> Sullivan PB, Juszczak E, Lambert BR, et al. Impact of feeding problems on nutritional intake and growth: Oxford Feeding Study II. *Dev Med Child Neurol* 2002;44:461-467
- <sup>99</sup> Gisel EG. Effect of oral sensorimotor treatment on measures of growth and efficiency of eating in the moderately eating-impaired child with cerebral palsy. *Dysphagia* 1996;11:48-58.
- <sup>100</sup> Pinnington L, Hegarty J. Effects of consistent food presentation on oral-motor skill acquisition in children with severe neurological impairment. *Dysphagia* 2000;15:213-223.
- <sup>101</sup> Rogers B. Feeding method and health outcomes of children with cerebral palsy. *J Pediatr* 2004;145:S28-32.
- <sup>102</sup> Brant CQ, Stanich P, Ferrari Jr. AP. Improvement in children's nutritional status after enteral feeding by PEG: an interim report. *Gastrointest Endosc* 1990;50:183-188.
- <sup>103</sup> Arvedson JC, Rogers BT. Pediatric swallowing and feeding disorders. *J Med Speech-Lang Pathol* 1993;1:203-221.
- <sup>104</sup> Gauderer MW. Percutaneous endoscopic gastrostomy: a 10-year experience with 220 children. *J Pediatr Surg* 1991;26:288-292.
- <sup>105</sup> Eyman RK, Grossman HJ, Chaney RH, Call TL. Survival of profoundly disabled people with severe mental retardation. *Am J Dis Child* 1993;147:329-336.
- <sup>106</sup> Ashwal S, Eyman RK, Call TL. Life expectancy of children in a persistent vegetative state. *Pediatr Neurol* 1994;10:27-33.
- <sup>107</sup> Strauss D, Kastner T, Ashwal S, White J. Tube-feeding and mortality in children with severe disabilities and mental retardation. *Pediatrics* 1997; 99:358-362.

- 
- <sup>108</sup> Del Giudice E, Staiano A, Capano G, et al. Gastrointestinal manifestations in children with cerebral palsy. *Brain Dev* 1999;21:307-311.
- <sup>109</sup> Fonkalsrud E. W., Foglia R. P., Ament M. E., et al. Operative treatment for the gastroesophageal reflux syndrome in children. *Journal of Pediatric Surgery* 1989;24(6):525-529
- <sup>110</sup> Okada T, Sasaki F, Asaka M, et al. Delay of gastric emptying measured by 13C-acetate breath test in neurologically impaired children with gastroesophageal reflux. *Eur J Pediatr Surg* 2005 Apr;15(2):77-81.
- <sup>111</sup> Li BU, Balint JP. Cyclic vomiting syndrome: evolution in our understanding of a brain-gut disorder. *Adv Pediatr*. 2000;47:117-160
- <sup>112</sup> Fitzpatrick E, Bourke B, Drumm B, et al. The incidence of cyclic vomiting syndrome in children: population-based study. *Am J Gastroenterol*. 2008;103:991-995
- <sup>113</sup> Drumm BR, Bourke B, Drummond J, McNicholas et al. Cyclical vomiting syndrome in children: a prospective study. *Neurogastroenterol Motil* 2012;24:922-927
- <sup>114</sup> Li BU, Misiewicz L. Cyclic vomiting syndrome: a brain-gut disorder. *Gastroenterol Clin North Am*. 2003;32:997-1019.
- <sup>115</sup> Boles RG, Adams K, Li BU. Maternal inheritance in cyclic vomiting syndrome. *Am J Med Genet A*. 2005 Feb 15;133A:71-77.
- <sup>116</sup> Wang Q, Ito M, Adams K, et al Mitochondrial DNA control region sequence variation in migraine headache and cyclic vomiting syndrome. *Am J Med Genet A*. 2004;131:50-58.
- <sup>117</sup> Li BU, Lefevre F, Chelimsky GG, et al. North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition consensus statement on the diagnosis and management of cyclic vomiting syndrome. *J Pediatr Gastroenterol Nutr*. 2008;47:379-393.
- <sup>118</sup> Sudel B, Li BU. Treatment options for cyclic vomiting syndrome. *Curr Treat Options Gastroenterol*. 2005;8:387-395.